Trajectories of functioning and mental health: determinants in general population

Ph.D. Dissertation presented by

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José Luis Ayuso Mateos, Catedrático de Psiquiatría de la Universidad Autónoma de Madrid, y Francisco Félix Caballero Díaz, profesor ayudante doctor de la Universidad Autónoma de Madrid, certifican que: Javier de la Fuente Carrillo, graduado en Psicología en la Universidad Complutense de Madrid, ha realizado la tesis doctoral titulada: "Trajectories of functioning and mental health: determinants in general population", considerando que este trabajo posee los méritos de originalidad, calidad, y rigor suficientes para hacerse acreedor al grado de doctor.

Y para que así conste autorizamos la presentación de esta tesis doctoral en la Universidad Autónoma de Madrid.

En Madrid a 26 de Agosto de 2019,

FDO: Dr. Francisco Félix Caballero Díaz

FDO: Prof. José Luis Ayuso Mateos

Index

Abstract

Introduction

Worldwide life expectancy has been increasing over the last five decades as a result of increases in life expectancy and reductions in fertility rates. Demographic projections predict dramatic increments in the percentage of people aged sixty and over, from about 11% in 2011, to over 20% in 2050. Considering the complex and heterogeneous dynamics of aging, there is a need for identifying determinants of health trajectories in general population. Such task requires using a holistic and robust framework that considers different domains of health,

Objectives

The objectives of this Ph.D. thesis are: 1) to develop a latent measure of health status based on domains of functioning that can be comparable across different longitudinal studies, identifying groups of the population with similar aging patterns and their associated sociodemographic and health-related determinants; 2) to analyze the roles of visual and hearing functioning as potential determinants of healthy cognitive aging, comparing rates of cognitive decline across different groups of sensory impairment; 3) to develop a sensory-cognitive latent measure to assess heterogeneous trajectories of sensory-cognitive difficulties and their associated risk factors; and 4) to assess and depict heterogeneous trajectories of depressive symptoms over the old age and associated determinants.

Methods

Person-centered and latent variable methods are used to assess heterogeneity in trajectories of functioning and mental health. A Bayesian multilevel Item Response Theory (IRT) approach is used to estimate a latent measure of health status that can be compared across the English Longitudinal Study of Ageing (ELSA) and the Health and Retirement Study (HRS). Growth Mixture Models (GMM) and Latent Class Mixed Models (LCMM) are used to identify finite sets of groups with heterogeneous trajectories of health, sensory-cognitive functioning, and depressive symptoms in older populations. A Structural Equation Modeling (SEM) approach is used to estimate the longitudinal latent associations between visual, hearing, and cognitive functioning. A longitudinal

measurement invariance model is used to estimate a latent measure of sensory-cognitive functioning. Receiver Operative Characteristic (ROC) curves are used to assess the predictive validity of the health metric and the sensory-cognitive measure in relation to mortality and dementia, respectively, using the Area Under the Curve (AUC).

Results

A common metric of health status was estimated using data from the ELSA and HRS studies. The metric presented good psychometric properties, with an adequate ability to predict mortality over 10 years in both ELSA (AUC = 0.74; 95% CI: 0.72, 0.75) and HRS (AUC = 0.74; 95% CI: 0.73, 0.75). Results from the GMM revealed four and five heterogeneous trajectories of health in the ELSA and HRS studies, respectively. In both studies, the presence of multiple chronic conditions, as well as low levels of education and household wealth, were associated with belonging to the classes with a worse trajectory of health. A longitudinal SEM model revealed that, visual ($\beta = 0.140$, $p < .001$) and hearing ($\beta = 0.115$, $p < .001$) difficulties predicted cognitive difficulties 8 years later. Increases in cognitive difficulties was steeper in people with visual impairment (Cohen's $d = 0.52$, $p < .001$), hearing impairment (Cohen's $d = 0.50$, $p < .001$), and dual-sensory impairment (Cohen's $d = 0.68$, $p < .001$) than those non-impaired (Cohen's $d = 0.12$, $p < .001$). The longitudinal measurement invariance SEM model revealed a second-order latent factor explained 32%, 36%, and 26% of the visual, hearing, and cognitive difficulties first-order factors variance over eight years, respectively. A latent measure of sensory-cognitive difficulties derived from the SEM model presented a good ability to predict dementia over ten years [AUC = 0.80; 95% IC = (0.75, 0.86)]. The LCMM model revealed three latent classes with heterogeneous trajectories of sensory-cognitive difficulties. Lower levels of education and wealth, as well as a greater presence of disability, self-reported medical diagnoses of diabetes, lower levels of physical activity, and higher depressive symptoms, were associated with worse sensory-cognitive trajectories. Three heterogeneous trajectories of depressive symptoms were identified by means of LCMM, representing a normative class, a subclinical trajectory class, and a chronic symptom trajectory. Increasing hearing difficulties and history of psychiatric problems were associated with the chronic symptom trajectory. Subclinical trajectories were associated with lower levels of education, history of psychiatric problems, and increasing visual difficulties. Clinical and subclinical classes presented a worse quality of life and satisfaction with life, as well as more disability, than the normative class.

Conclusions

Some socioeconomic and health related factors are common determinants of functioning and mental health. In that regard, a higher education and wealth are positively associated with functional ability, cognitive function, and affect. On the contrary, the presence of multiple chronic conditions, as well as visual and hearing impairment are associated with both cognitive and affective disorders.

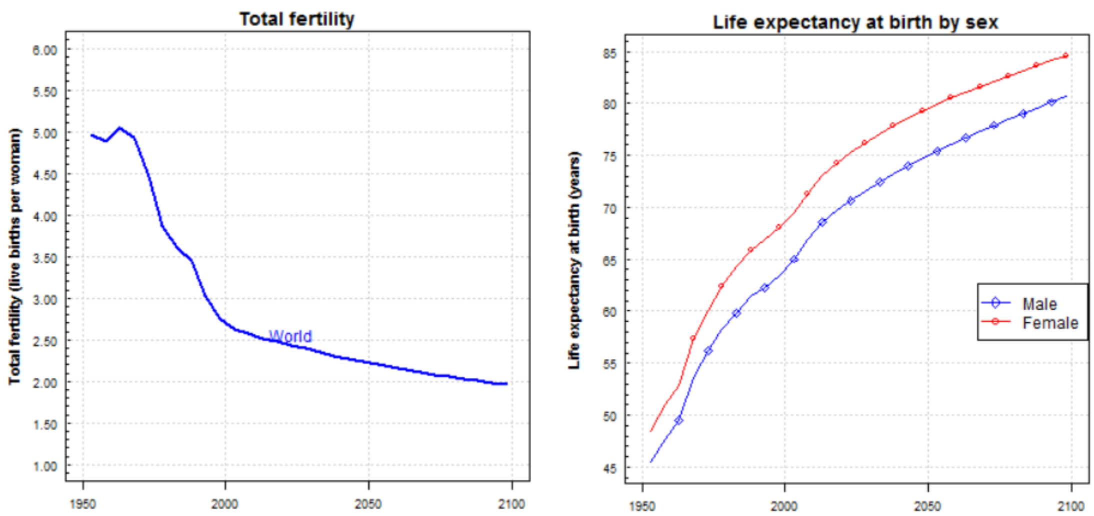
1. Introduction.

1.1. Conceptualization and measurement of health

1.1.1. Aging and health: a conceptual framework

Worldwide population is aging steadily. By 2050, a 21% of the world population will be over 60 years (Chatterji, Byles, Cutler, Seeman, & Verdes, 2015). Life expectancy has been continuously increasing over the past 5 decades all over the world. Whereas in low- and middle-income countries this increase has been mainly fostered by reductions of mortality rates in early stages of the lifespan, on high-income countries mortality rates have been reduced among the elderly (WHO, 2015). It has been proposed that increased survival among the older population in high-income countries might be a result of better health care services, public health initiatives, and birth-cohort changes in life-style (WHO, 2015).

Figure 1. Worldwide fertility rates, and worldwide life expectancy at birth by sex (United Nations, 2017).



From a biological standpoint, aging is a multifactorial process involving a gradual accumulation of molecular and cellular damage over time. The cellular deterioration resulting from the aging process encompasses relentless physiological changes associated with declines in physical and cognitive capacities (Beard et al., 2016), increasing the risk of diverse health conditions and eventually death (Miller, 2009). One of the most widely accepted theories on cellular aging is based on telomere shortening over the lifespan (Zhu, Liu, Ding, Wang, & Geng, 2019). Telomeres are specific deoxyribonucleic acid (DNA) sequences located at the end of the chromosomes, involved in the stabilization of chromosomal ends. Telomeres are synthesized by an enzyme called telomerase, which suffers a depletion as result of the aging process, leading to telomeres shortening. Telomeres shortening can eventually produce translocations, mutations, or fusions of the specific DNA sequences damaged, thus increasing the risk of illness and death (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003).

Despite the relentless nature of the aging process, there is a remarkable variability in the dynamics of aging (Hsu & Jones, 2012). People age differently, and life-course trajectories of health are variable across individuals. Whereas some people in their sixties might present severe disability and multiple chronic conditions, others can preserve an active lifestyle, being free of disability in later stages of their life.

Moreover, the relationship between chronological age and health status might also vary depending on the conceptualization of health status itself. For example, imagine a 70 years old person presenting hearing impairment. Without hearing aid this person might find difficulties following conversations, which in turn could have a negative impact on the quality and quantity of social interaction, eventually triggering feelings of loneliness and social isolation. Most likely, social interactions will not be affected if this person would use a hearing aid. Therefore, the mere presence of health conditions would not be a good indicator of health status, since its impact on people's lives might be completely different depending on diverse contextual and environmental factors (Cieza et al., 2015).

Considering the variability in the aging process, as well as the current scenario of population aging, it is crucial to provide a common conceptual framework for measuring and understanding the complex dynamics of aging. In that regard, the World Health Organization (WHO) (World Health Organization, 2001) and the International Classification of Functioning (ICF) (Salomon et al., 2003) have provided a holistic framework for the measurement of health. This framework focuses on a life-course approach based on health trajectories and the concept of functional ability, understanding health as an intrinsic and multidimensional attribute composed by several domains of functioning (e.g., mobility, cognition, vision, hearing, etc.).

The concept of functional ability refers to the interaction between the physical and mental capacities of an individual (i.e., intrinsic capacity) with the environmental factors composing the context where the individual lives in (WHO, 2015). Thus, older people presenting low levels of intrinsic capacity could still preserve a good functional ability by means of facilitating environmental factors. For example, open-air public spaces with ramps instead of steps might facilitate people with mobility difficulties to maintain themselves physically active. On the other hand, some environmental factors might act as barriers for functional ability, thus resulting in health inequalities among people with similar intrinsic capacity. For example, discrimination against older people in the labor market might force people retiring prematurely, which might have an impact on subsequent individual differences in diverse psychological, socioeconomic, and health-related outcomes.

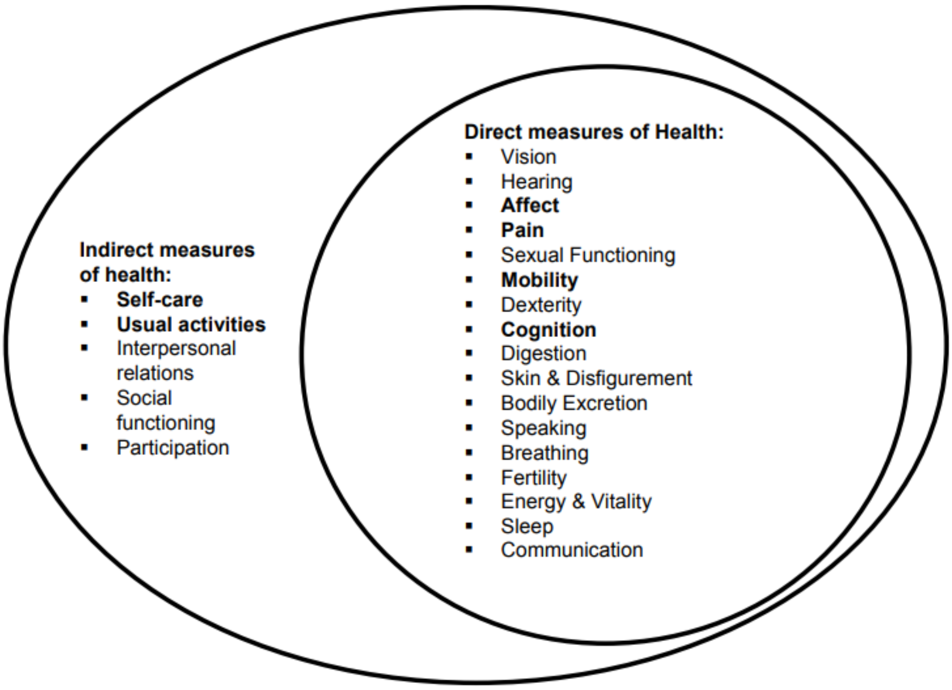
1.1.2. The measurement of health

Based on the conceptual framework proposed by the WHO (WHO, 2001) and the ICF (Stucki, 2005), an appropriate measure of health status would require the quantification of the functional ability of an individual (Salomon et al., 2003). To do so, it is necessary to identify and assign cardinal measures to the different domains of functioning that compose the overall health status of an individual. The identification of the important domains comprising the overall construct of functional ability is one of the key challenges in the measurement of health. In that regard, Solomon et al. (2003) proposed three categories of domains of functioning based on their relative importance (Figure 2):

- A set of core domains commonly agreed to be direct measures of health (in bold).
- Direct measures of health complementary to the main core of direct measures.
- Indirect measures of health.

As can be seen in Figure 2, self-care, usual activities, affect, pain, mobility, and cognition are considered as core domains of health, and are usually included in most generic measures of health. Typically, the assessment of the different domains of functioning underlying overall health status are conducted by means of self-reported items indicating the presence of difficulties on a given domain, or measured tests of capacity (e.g., tests of cognitive performance, walking speed, or grip strength). Ideally, these measures could be aggregated into a single numeric index with scalar properties defining the overall health status of an individual. Likewise, this single measure could be then aggregated at a population level, allowing assessing and comparing potential heterogeneous trajectories of health among individuals and populations.

Figure 2. Domains of functioning proposed by the World Health Organization (Solomon et al., 2003).



Some recent studies have developed health status measures under this framework. Using an Item Response Theory (IRT) approach, Cieza et al., (2015) estimated a cross-sectional health measure based on self´-reported questions and measure tests covering a wide range of domains of functioning, such as cognition, affect, mobility, activities of daily living (ADLs), or instrumental activities of daily living (IADLs) among others. This measure was estimated separately in two nationally representative samples from the English and the US populations, using an IRT approach over the common items of both studies. They compared the health status between the English and the US populations using both the latent health measure and the prevalence of health conditions. Results showed a worse health status in the US sample when using the prevalence of health conditions. However, when using the latent health metric, the differences in terms of health status between the English and US populations disappeared. These results highlight some potential limitations derived from using only prevalence of health conditions for assessing and comparing health across populations, since this approach does not take into account the severity of the health conditions considered.

In another study Caballero et al., (2017) developed another latent health measure based on domains of functioning, but using longitudinal data from the first six waves of the English Longitudinal Study of Ageing (ELSA). In this case a Bayesian multilevel IRT approach was used to estimate the health measure, which allowed for considering both anchor and wave-varying items. The health measure presented appropriate psychometric properties, and a good ability to predict mortality over ten years. Authors conclude that this methodological approach would allow for creating a common health measure across epidemiological studies, enabling the assessment and comparison of health trajectories over time and across studies.

Considering previous efforts on development health measures based on domains of functioning, future research should be conducted to apply similar procedures in harmonized datasets comprising several longitudinal studies. This is a crucial task that should be covered in order to properly monitor health trajectories in a comparable way across epidemiological studies with different design and measurement features.

1.1.3. Determinants of healthy aging in general population

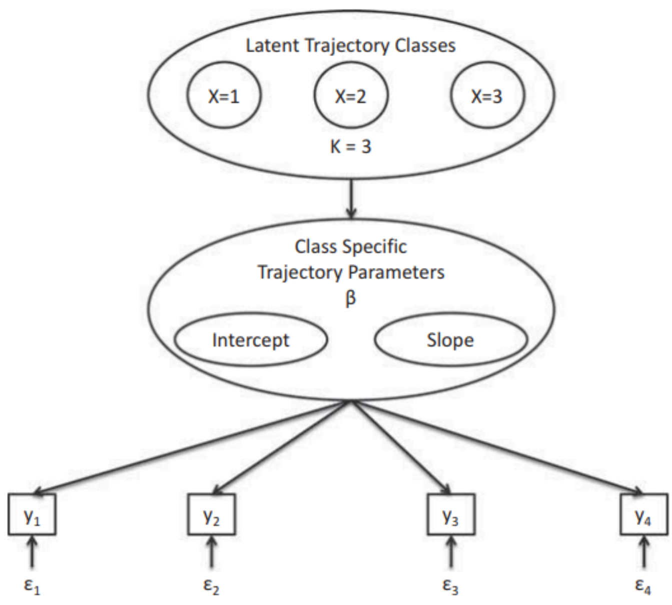
Healthy aging could be conceptualized as “the process of developing and maintaining the functional ability that enables well-being in older age” (WHO, 2003). According to this point of view, the measurement of healthy aging would require assessing health trajectories over time.

As mentioned previously, there is a great variability in the aging pathways. Several studies have shown heterogeneous trajectories of health, providing evidence on determinants or factors associated with these trajectories (Cadar, Davies, Llewellyn, Batty, & Steptoe, 2018; Cosco, Muniz, Stephan, & Brayne, 2014; García-Esquinas et al., 2019; Jones, Ledermann, & Fauth, 2018). According to a recent systematic review on risk factors associated with healthy aging, aging pathways are affected by exposure to different life-styles, as well as diverse biological, psychological and social risk factors over the lifespan (Kralj et al., 2018). The 65 studies included in this review allowed for identifying several modifiable determinants of healthy aging. For example, among biological and health related factors, body mass index was found to be the most frequently examined determinant. Regarding behavioral modifiable risk factors, smoking, low levels of physical activity, and unhealthy dietary habits were identified as the factors most consistently associated with a worse trajectory of health. Finally, depression and impaired cognitive functioning were robustly associated with several adverse health conditions, highlighting the importance of mental health as a determinant of healthy aging. A better understanding of how these factors influence functional ability over time could help to optimize health interventions and promote well-being in old age.

On the other hand, whether increase in life expectancy is accompanied by a better functional ability in the last stages of the lifespan is not fully clear. Recent cohorts are living longer, but are they aging in a better manner? Whereas some studies have reported increases in the prevalence and incidence of chronic conditions in older population (Chatterji et al., 2015; United Nations, 2015), others evidence significant decreases in functional difficulties and disability in recent cohorts (Crimmins, Hayward, Hagedorn, Saito, & Brouard, 2009; Moe & Hagen, 2011; Sagardui-Villamor, Guallar-Castillón, García-Ferruelo, Banegas, & Rodríguez-Artalejo, 2005).

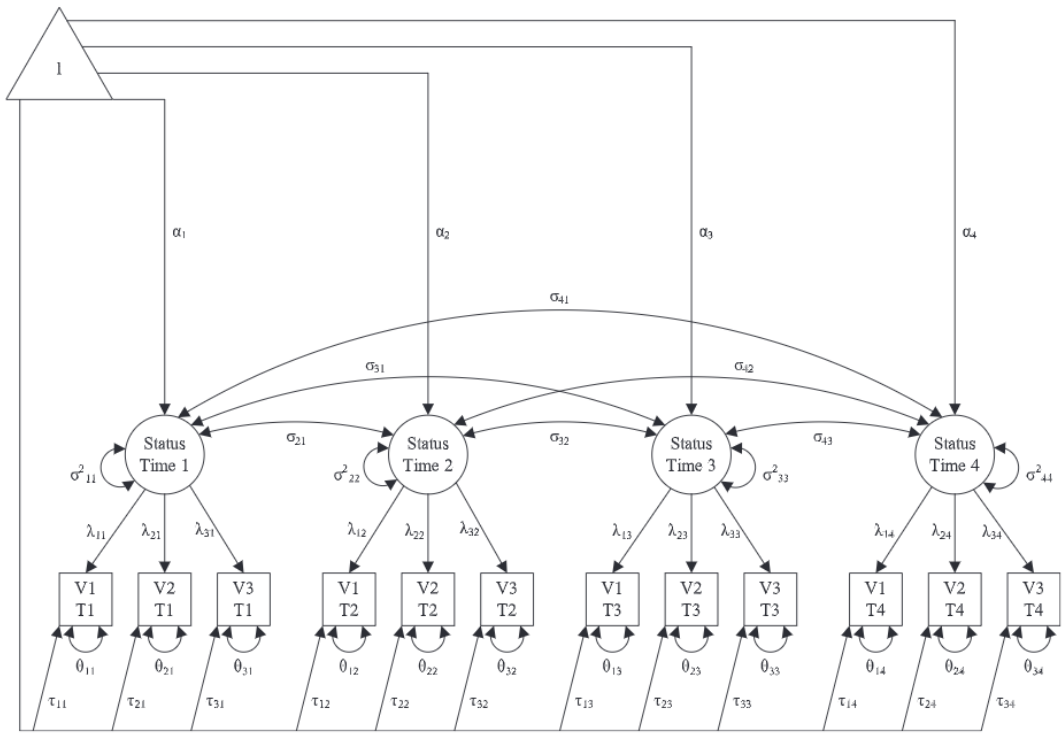
In order to assess trajectories of health, appropriate methods focusing on between-person differences in intra-individual change are needed. For that purpose, two main statistical approaches are proposed and used in this thesis, namely Growth Mixture Modeling (GMM) and Structural Equation Modeling (SEM). GMM allows identifying *k* unobserved or latent groups of a population presenting similar trajectories on a response variable *y*, thus, allowing the estimation of population parameters reflecting intra-individual change β, heterogeneity in intra-individual change across latent classes, and shape of the change (Ram & Grimm, 2009). For a graphical representation of GMM see Figure 3.

Figure 3. Representation of a 3-class GMM (van den Bergh & Vermunt, 2018).



SEM models allow assessing temporal change on a latent factor reflecting a theoretical construct. Figure 4 displays a longitudinal confirmatory factor model comprised of twelve observed indicators tapping a latent factor measured in four times. Parameters α_{1-4} represent mean scores on the latent factor in times 1 to 4. Using a multi-group factorial invariance approach, it is possible to estimate and constrain α parameters across observed groups (e.g., men and women, different countries, etc.), allowing assessing potential inter-group differences in intra-individual change.

Figure 4. Longitudinal confirmatory factor model comprising three variables tapping a single latent factor assessed four times (Widaman, Ferrer, & Conger, 2010).



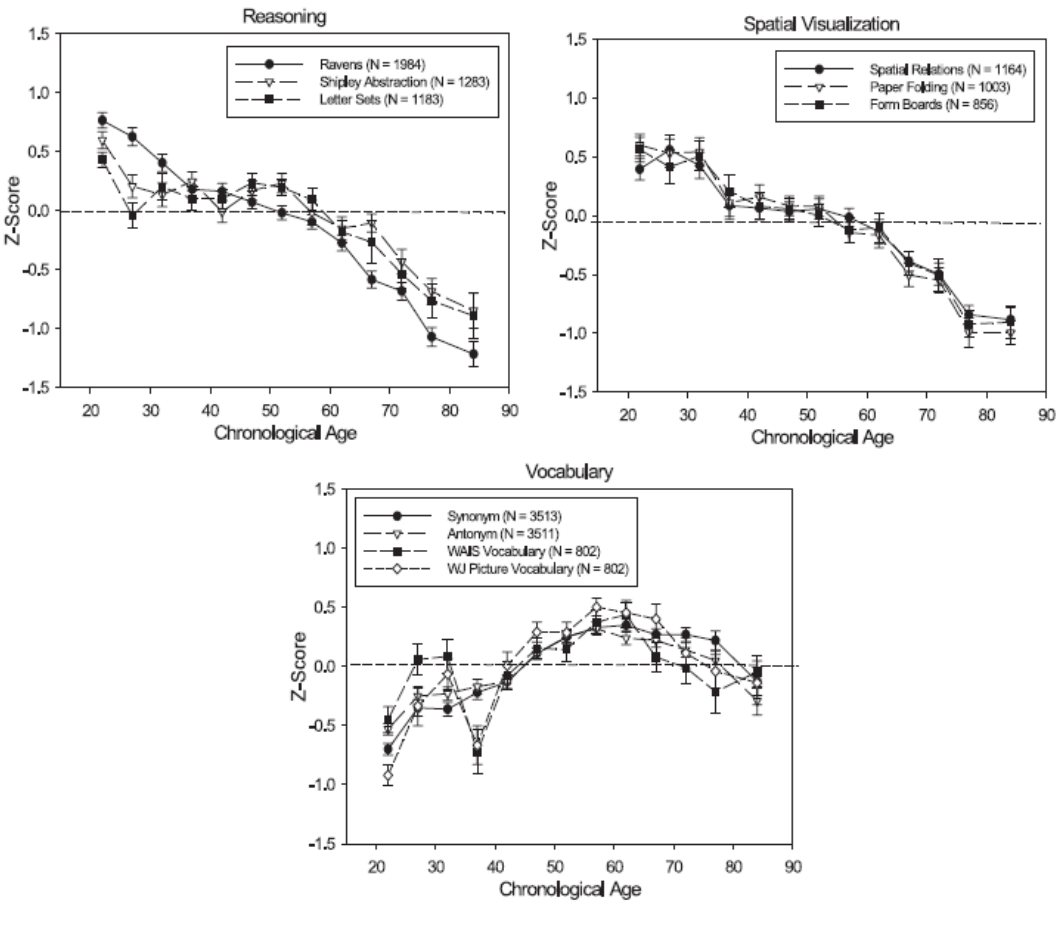
1.2. Trajectories of mental health

As mentioned previously, and in accordance with the WHO conceptualization of health, cognition and affect are two dimensions of mental health considered as direct measures and core domains of functional ability. According to the Global Burden of Disease, up to 25% of all disability-adjusted life-years, a measure indicating the years living with disability and years of life lost, are accounted for neuropsychiatric conditions (Mathers & Loncar, 2006). However, mental health has been overlooked, and its connection with other health conditions underestimated (Prince et al., 2007). Understanding age-related changes in these specific domains of mental health, as well as their determinants, are key challenges for enhancing health trajectories and promoting healthy aging.

1.2.1. Cognitive aging

Cognitive functioning experiences a progressive decline as a result of the aging process in general population. Such change typically starts during middle adulthood affecting specific domains of fluid cognition, such as abstract and visuospatial reasoning, episodic memory, or processing speed (Salthouse, 2004). On the contrary, age-related decline in crystallized cognition, such as verbal knowledge, is less pronounced. Figure 5 displays the relationship between different measured tests of fluid cognition (abstract reasoning, and spatial visualization) and crystallized cognition (vocabulary) with chronological age.

Figure 5. Mean performance across different ages in fluid and crystalized cognitive tests (from Salthouse, 2004).



Despite the different paces of decline across domains of cognition, there is evidence indicating the structure of cognitive aging is mainly unidimensional. Recently, Tucker-Drob, Brandmaier, and Lindenberger (2019) meta-analyzed 89 effect sizes of shared variations in longitudinal change across different domains of cognitive performance. They identified a general factor of cognitive aging explaining 60% of the variance of cognitive changes, increasing from near 45% at age 35 to 70% at age 80.

Several studies show that normative cognitive aging is highly heritable (Finkel & Reynolds, 2009; Johnson, McGue, & Deary, 2013). According to a review of cross-sectional twin research conducted by Johnson, McGue and Deary (2013) the heritability of general cognitive performance in late life ranges between 50% and 80%. Although genetic influences on cognitive aging are moderate to strong, there is still room for environmental factors. In that regard, there is evidence indicating that some social and biological factors might have a significant impact on cognitive aging.

Among social moderators of normative cognitive aging, education levels and years of education have been associated with better performance on different cognitive tasks, and even with a slow pace of cognitive decline. These factors are usually employed as proxy indicators of cognitive reserve, which is associated with higher levels of cognitive functioning among older people. According to Stern (2002), cognitive reserve would reflect a more efficient use of brain networks which in turn would play a protective role against age-related cognitive decline. However, Tucker-Drob, Johnson, and Jones (2009) showed that, in older adults, years of education and vocabulary knowledge were positively associated with levels of cognitive functioning, but not slopes of cognitive decline. Results from this latter study indicate that cognitive reserve would reflect the persistence of preexistent differences in the levels of cognitive functioning, but not differential rates of cognitive decline.

Some biological factors have also been associated with normative cognitive aging. From the first study conducted by Lindenberger and Baltes (1994), several cross-sectional and longitudinal studies have evidenced a link between sensory and cognitive functioning in the old age (Humes & Young, 2016; Roberts & Allen, 2016; Wayne & Johnsrude, 2015). Although the relationships between these domains of functioning are well documented, the mechanisms underlying this relationship is not completely clear yet.

According to the sensory deprivation hypothesis there is a causal pathway by which impairments in sensory functioning reduce the quality of the stimuli input, which in turn has long-term negative effects on cognitive functioning due to neural atrophy. In that regard, some longitudinal studies have shown steeper declines in cognition in older people presenting visual and/or hearing problems (Fischer et al., 2016; F. R. Lin et al., 2014; Maharani, Dawes, Nazroo, Tampubolon, & Pendleton, 2018). Moreover, sensory dysfunction has also been associated with greater odds of developing some forms of dementia disease (Chen, Bhattacharya, & Pershing, 2017; Luo et al., 2018). Altogether, previous literature highlights the importance of understanding the mechanisms by which sensory functioning might moderate age-related cognitive decline.

From a correlational approach, the common cause hypothesis posits that cognitive and sensory functioning are associated in the older population because they both depend on the neurophysiological integrity of the brain, which gradually declines during the aging process (Roberts & Allen, 2016). Thus, a common neurodegenerative process affecting both cognition and perception would account for the observed association between these domains of functioning. In that regard, there is evidence indicating that some neurobiological alterations due to the aging process affect both sensory and cognitive functioning (Chang et al., 2015; Harris & Dubno, 2017). In addition, it has been highlighted the potential role of cardiovascular disease and inflammatory processes in relation to the sensory-cognitive link observed in older people (Whitson et al., 2018). However, evidence is needed to better understand the nature of the common etiology of sensory-cognitive function, as well as to identify potential common determinants of these domains in general population.

1.2.2. Depressive symptoms in the old age

As cognition, affect is a core domain of functioning and a direct measure of health status (Salomon et al., 2003). Some affective disorders, like depression, are highly prevalent in the old age. Evidence shows that near 30% of older people experience depressive symptoms at a clinical level (Andreas et al., 2017). Depression in the old age is associated with many adverse health related outcomes, being a risk factor for a worse functioning and quality of life, and even increased mortality, among others (Chui, Gerstorf, Hoppmann, & Luszcz, 2015; Luppa et al., 2012).

According to the systematic review conducted by Musliner, Munk-Olsen, Eaton, and Zandi (2016), long-term trajectories of depressive symptoms are heterogeneous, with a remarkable variability in terms of severity and stability. Following a GMM approach, they identified up to four heterogeneous trajectories of depressive symptoms across 25 studies. Although most of the participants across studies did not present significant levels of depressive symptoms, a small proportion (less than 10%) experienced stable high levels of depressive symptomatology. It is important to note the remarkable variability on the number of heterogeneous trajectory classes of depressive symptoms, as well as the fact that in many occasions the representativeness of older population is overlooked.

Previous studies have identified different sociodemographic and health-related factors predicting the evolution of depressive symptomatology in the old age. Among all, sex differences is the most consistently reported, with women presenting both higher levels and steeper increases in depressive symptomatology over the old age (Carrière et al., 2017; Chui et al., 2015). Among sociodemographic factors, both lower education and household income predict a worse trajectory of depressive symptomatology (Hybels, Landerman, & Blazer, 2013; Montagnier et al., 2014). Some health-related factors, such as sensory problems or a history of psychiatric problems also have a negative impact on depressive symptoms trajectories (Hsu, 2012; Tolman, Hill, Kleinschmidt, & Gregg, 2005). Despite the available evidence, the time-varying nature of some determinants of the course of depression (such as the accumulation of chronic conditions over the old age) has been disregarded.

1.3. Summary of gaps in knowledge

Previous literature suggests two important gaps in knowledge regarding the definition and measurement of health levels at both individual and population levels. The lack of a common conceptual framework for defining and measuring health status hinders the comparability of health trajectories across populations. This shortcoming must be addressed to shed light into the intricate and heterogeneous aging pathways, considering both general functional ability and specific domains of health.

A better understanding of aging is imperative to enhance health trajectories and optimize well-being in the old age, especially considering the rapid aging of worldwide population. To do so, it is necessary to develop and validate common measurement approaches allowing for assessing and comparing health trajectories of older people over time and across populations at different levels of specificity. Such measurement approaches should be based on different domains of functioning, rather than health conditions only. In addition, robust methodological approaches are required for identify different patterns of healthy aging and their determinants. In that regard, Study I of the present thesis addresses these issues, proposing a methodological framework for 1) developing a common measure of health based on domains of functioning that can be compared over time and across studies, and 2) a methodological approach allowing for identifying different patterns of healthy aging and associated determinants.

As previously mentioned, cognition is a core domain of health that requires special attention in older population. The identification of determinants and mechanisms associated with healthy cognitive aging is a key issue for promoting and enhancing functionality and well-being in the older population. Although the heritability of cognitive aging is large, there are some potentially modifiable factors, like visual or hearing functioning, that might moderate rates of cognitive decline in general population. Therefore, understanding the mechanisms underlying the well documented association between sensory functioning and cognition in the old age is a gap in knowledge that needs to be covered. Studies II and III included in this thesis address this question. On the one hand, Study II provides evidence on the roles of visual and hearing impairments as early determinants of subsequent cognitive aging, providing evidence on the sensory deprivation model. On the other hand, Study III aims at developing a common measure of sensory-cognitive functioning that could be used to identify potential common determinants of visual, hearing and cognitive functioning in older population.

The last gap in knowledge this thesis aims to fill concerns affect, another core domain of health that commonly experiences disorders over the old age. There is scarce evidence and remarkable heterogeneity in the literature with regards to the heterogeneous trajectories of depressive symptomatology in the old age. Covering this issue is of especial importance considering the high prevalence of clinical and subclinical levels of depressive symptomatology, and their association with other relevant health-related outcomes. Therefore, Study IV aims at assessing heterogeneous trajectories of depressive symptomatology in older population, focusing on identifying time-varying determinants of those trajectories, as well as their association with subsequent health-related outcomes.

To sum up, this thesis aims at assessing healthy aging and its determinants, with special focus on two core domains of health: cognition and affect. To do so, a robust methodological framework is proposed, comprising sophisticated statistical methods allowing for identifying different patterns of healthy aging.

This work is integrated within the Ageing Trajectories of Health: Longitudinal Opportunities and Synergies (ATHLOS) project (http://athlosproject.eu/), an EU-funded project which aims to generate an harmonized data set comprising several international longitudinal studies and to achieve a better understanding of the impact of aging on health by developing a new single measure of health status (Sanchez-Niubo et al., 2019). The English Longitudinal Study of Ageing (ELSA) (Steptoe, Breeze, Banks, & Nazroo, 2013) and the Health and Retirement Study (HRS) (Sonnega et al., 2014) surveys collected data in the English and US populations, respectively, and have been included in the harmonized ATHLOS data set. The analyses showed in the present work have been conducted using data from both longitudinal surveys.

2. Objectives and hypothesis

General objective

The overall aim of this thesis was to assess trajectories of functioning and mental health in general population, and to identify determinants associated with those trajectories.

Specific objectives and hypotheses

Determinants of health trajectories in general population (Study I)

Objectives

To identify different patterns of healthy aging in a harmonized dataset comprising two large representative samples of the US and the English populations.

- To develop a latent measure of health status based on domains of functioning that can be comparable across different longitudinal studies.
- To identify groups of the population with similar aging patterns, and to identify sociodemographic and health-related determinants of these trajectories.

Hypotheses

- The latent measure of health status will present appropriate reliability and a good ability to predict mortality.
- Several latent classes with heterogeneous trajectories of health will be identified in both samples.
- Low levels of education and wealth, and the presence of chronic conditions will be identified as determinants of a worse trajectory of health.

Objectives

To analyze the roles of visual and hearing functioning as potential determinants of healthy cognitive aging.

- To assess the predictive ability of visual and hearing functioning on cognitive functioning eight years later.
- To compare rates of cognitive decline across groups of sensory impairment (i.e., hearing impairment, visual impairment, and dual sensory impairment).

Hypotheses

- Visual and hearing difficulties are associated with subsequent cognitive difficulties.
- People presenting sensory impairment (i.e., hearing impairment, visual impairment, and dual sensory impairment) present a steeper decline in cognitive functioning.

Objectives

To develop a sensory-cognitive latent measure based on the common cause hypothesis in older population to assess heterogeneous trajectories of sensory-cognitive difficulties and their associated risk factors:

- To assess the latent structure of sensory-cognitive aging, with special focus on the longitudinal factorial invariance of a common factor explaining visual, hearing, and cognitive functioning.
- To develop a latent measure of sensory-cognitive difficulties based on the common cause hypothesis, providing evidence on its predictive ability.
- To identify groups of the population with heterogeneous trajectories of sensory-cognitive difficulties.
- To identify sociodemographic and health-related determinants of the trajectory classes.

Hypotheses

- The common cause latent factor will present longitudinal factorial invariance.
- The sensory-cognitive latent measure derived from the common cause model will present a good ability to predict dementia over time.
- At least one latent class presents high and stable trajectories of sensory-cognitive difficulties over the follow-ups.
- Latent classes presenting high or stable sensory-cognitive difficulties will be associated with cardiovascular risk factors.

Determinants of mental health: trajectories of depressive symptoms in old age (Study IV)

Objectives

To assess and depict heterogeneous trajectories of depressive symptoms over the old age, and to identify associated determinants.

- To identify groups of the older population with heterogeneous trajectories of depressive symptoms.
- To identify sociodemographic and health-related determinants of the trajectory classes.
- To assess the predictive role of the trajectory classes in relation to subsequent healthy aging outcomes.

Hypotheses

- There are various latent classes with heterogeneous trajectories of depressive symptomatology.
- The majority of participants do not present clinically significant depressive symptomatology.
- At least one latent class presents high and stable trajectories of depressive symptoms over the follow-ups.
- Latent classes presenting clinically significant depressive symptomatology will present worse quality of life and functioning over time.

3. List of publications

Study 1. de la Fuente, J., Caballero, F. F., Sánchez-Niubó, A., Panagiotakos, D. B., Prina, A. M., Arndt, H., ... & Ayuso-Mateos, J. L. (2018). Determinants of Health Trajectories in England and the United States: An Approach to Identify Different Patterns of Healthy Aging. *The Journals of Gerontology: Series A*, 73, 11, 1512-1518, doi: 10.1093/gerona/gly006.

Study 2. de la Fuente, J., Hjelmborg, J., Wod, M., de la Torre-Luque, A., Caballero, F. F., Christensen, K., & Ayuso-Mateos, J. L. (2018). Longitudinal Associations of Sensory and Cognitive Functioning: A Structural Equation Modeling Approach. *The Journals of Gerontology: Series B*, gby147*,* doi: 10.1093/geronb/gby147.

Study 3. de la Fuente, J., Moreno-Agostino, D., de la Torre-Luque, A., Prina, A.M., Haro, J.M., Caballero, F.F., & Ayuso-Mateos, J.L. (2019). Development of a combined sensory-cognitive measure based on the common cause hypothesis: heterogeneous trajectories and associated risk factors. *The Gerontologist*,

Study 4. de la Torre-Luque, A., de la Fuente, J., Prina, M., Sanchez-Niubo, A., Haro, J. M., & Ayuso-Mateos, J. L. (2019). Long-term trajectories of depressive symptoms in old age: Relationships with sociodemographic and health-related factors. *Journal of affective disorders*, *246*, 329-337, doi: 10.1016/j.jad.2018.12.122.

4. Summary of results

4.1. Determinants of health trajectories in general population (Study I)

In Study I of this thesis, a common metric of health status was estimated using data from the ELSA and the HRS studies. The metric presented good psychometric properties, with an adequate ability to predict mortality over 10 years in both ELSA (AUC = 0.74; 95% CI: 0.72, 0.75) and HRS (AUC = 0.74; 95% CI: 0.73, 0.75). As can be seen in Table 1, the metric was also sensitive to aging, with significant heterogeneity in the wave coefficient across individuals.

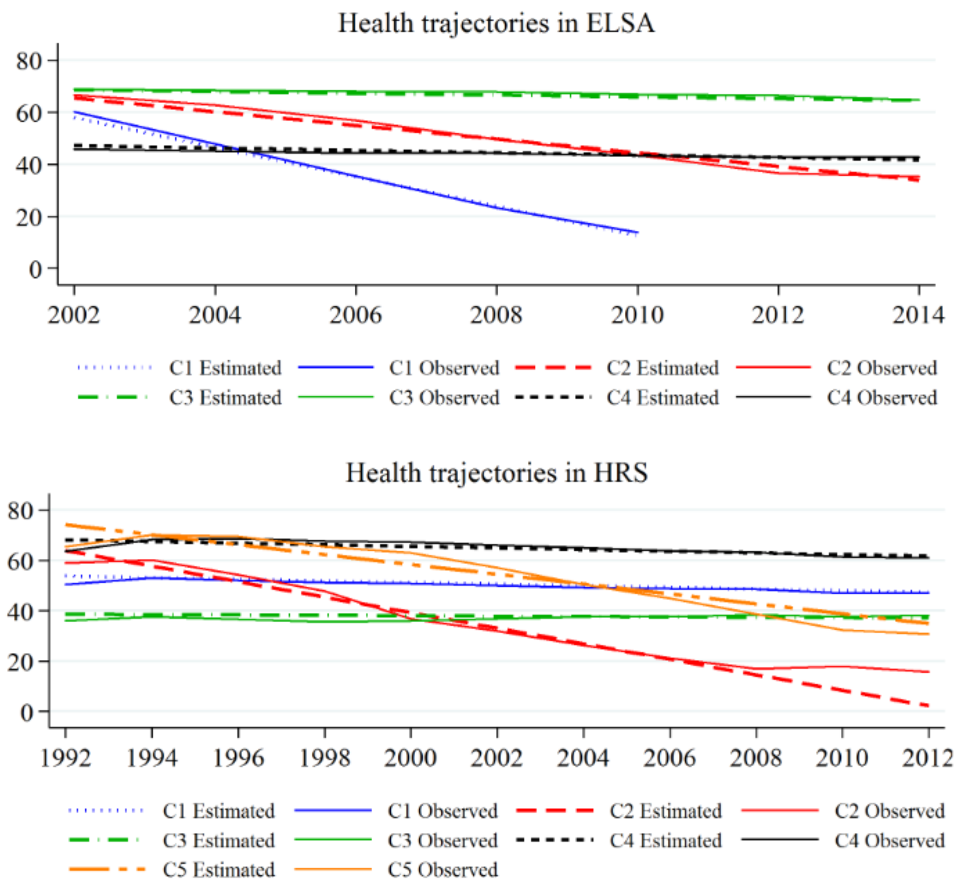
Table 1. Mixed-effect multilevel regression to assess the relationship between age and health, after adjusting for other covariates.

Fixed effects	Coef.	S.E.	95% CI	
Intercept	69.16	0.26	68.65	69.68
Wave	-0.37	0.01	-0.39	-0.35
Sex (ref. Men)	-2.87	0.10	-3.06	-2.68
Study (ref. ELSA)	-2.26	0.10	-2.46	-2.05
Age group (ref. 18 - 49)				
50 - 59	-0.99	0.12	-1.22	-0.76
60 - 69	-1.76	0.13	-2.01	-1.50
70 - 79	-4.80	0.14	-5.07	-4.53
80 - 89	-10.47	0.15	-10.77	-10.17
90+	-18.97	0.21	-19.38	-18.56
Random Effects				
Level 2: Subject	Coef.	S.E.	95% CI	
Wave	1.25	0.01	1.23	1.27
Intercept	11.50	0.06	11.39	11.61
Residual	6.78	0.01	6.75	6.80
τ_{01}	-0.44	0.01	-0.46	-0.43

Note: τ_{01} = correlation between intercept and wave slope.

The health status measure created was then used to assess trajectories of healthy aging. Results from the GMM revealed four and five heterogeneous trajectories of health in the ELSA and HRS studies, respectively (Figure 6).

Figure 6. Health trajectories by class identified by means of GMM in the ELSA and HRS studies.

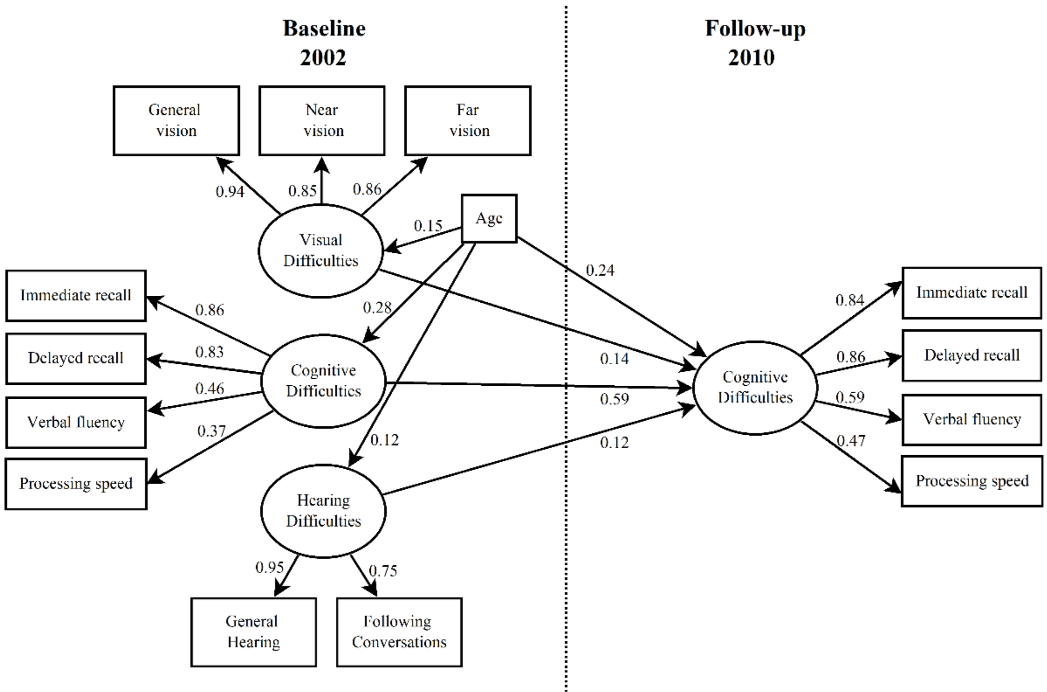


In both studies, the presence of multiple chronic conditions, as well as low levels of education and household wealth, were associated with belonging to the classes with a worse trajectory of health (steeper decline or lower level).

4.2. Determinants of mental health: sensory deprivation and cognitive aging (Study II)

In Study II, a Structural Equation Model (SEM) was used to assess the longitudinal associations of visual and hearing difficulties with cognitive difficulties eight years later. After controlling the potential confounding effect of cognitive difficulties at baseline, visual (β = 0.140, p < .001) and hearing (β = 0.115, p < .001) difficulties predicted cognitive difficulties 8 years later (see Figure 7).

Figure 7. Structural Equation Model assessing the longitudinal associations of visual and hearing difficulties with subsequent cognitive difficulties.

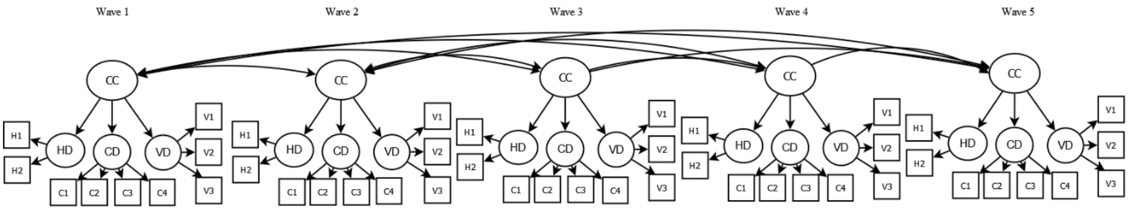


Results from a longitudinal and multi-group measurement invariance model in the cognitive difficulties factor revealed the latent increase in cognitive difficulties was steeper in people with visual impairment (Cohen's d = 0.52, p < .001), hearing impairment (Cohen's d = 0.50, p < .001), and dual-sensory impairment (Cohen's d = 0.68, p < .001) than those non-impaired (Cohen's d = 0.12, p < .001).

4.3. Determinants of mental health: common cause hypothesis (Study III)

The common cause measurement model achieved longitudinal factorial invariance [goodness-of-fit indices: TLI=0.989; CFI=0.991; RMSEA=0.026], with a common latent factor explaining 32%, 36%, and 26% of the visual, hearing, and cognitive difficulties first-order factors variance over eight years, respectively (see Figure 8).

Figure 8. Common cause model for explaining the relationships between hearing, visual, and cognitive difficulties.

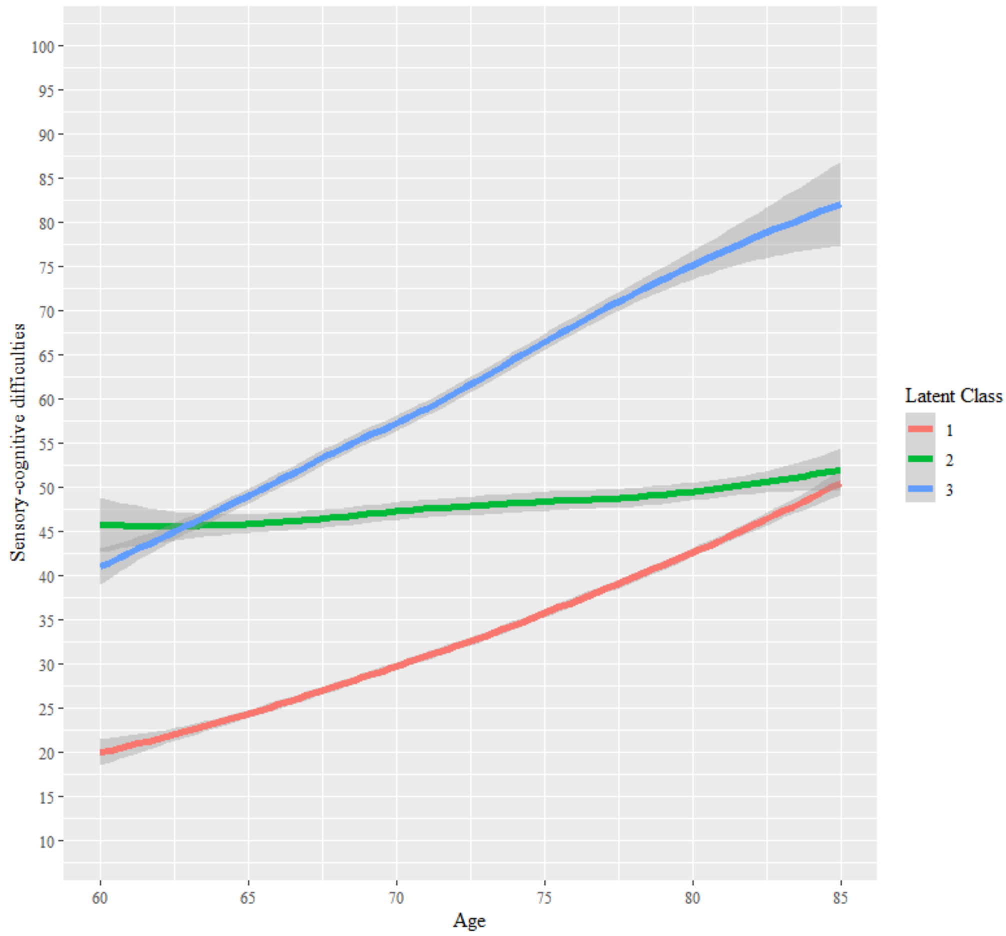


Note: CC = Common cause; HD = Hearing Difficulties; CD = Cognitive difficulties; VD = Visual Difficulties.

The latent measure of sensory-cognitive difficulties derived from the common cause measurement model presented a good ability to predict incident dementia over ten years [AUC = 0.80; 95% IC = (0.75, 0.86)].

Results from the latent class mixed model (LCMM) revealed three latent classes with heterogeneous trajectories of sensory-cognitive difficulties (see Figure 9). A modal class comprising 73.44% of the overall sample was identified. This class presented the lowest sensory-cognitive difficulties at baseline (Intercept = 11.88, $p<0.001$), and a significant slope with both linear ($\beta=1.27$, $p<0.001$) and quadratic ($\beta=0.02$, $p<0.001$) shape. Class 2 comprised 14.72% of the sample, and presented a stable trajectory of heightened sensory-cognitive difficulties. This trajectory class presented the highest levels of sensory-cognitive difficulties at baseline (Intercept = 39.29, $p<0.001$), and a small but significant quadratic shape ($\beta=0.02$, $p<0.001$). Finally, Class 3 comprised 11.84% of the sample, and featured the highest linear slope ($\beta=1.55$, $p<0.001$).

Figure 9. Trajectories of the combined sensory-cognitive difficulties latent score by class.



Considering the modal class (Class 1) as reference, Classes 2 and 3 comprised more female participants, and were associated with lower levels of education and wealth, as well as a greater presence of ADLs and IADLs difficulties, self-reported medical diagnoses of diabetes, lower levels of physical activity, and higher *Center for Epidemiologic Studies – Depression* (CESD) score, indicating higher levels of depressive symptoms (see Table 2). Class 2 presented older participants compared with the modal class, individuals comprising Class 3 were more likely to be younger. In addition, Class 3 presented a significantly higher proportion of people with high blood pressure

Table 2. Multinomial logistic regression model for predicting sensory-cognitive classes identified in the LCMM.

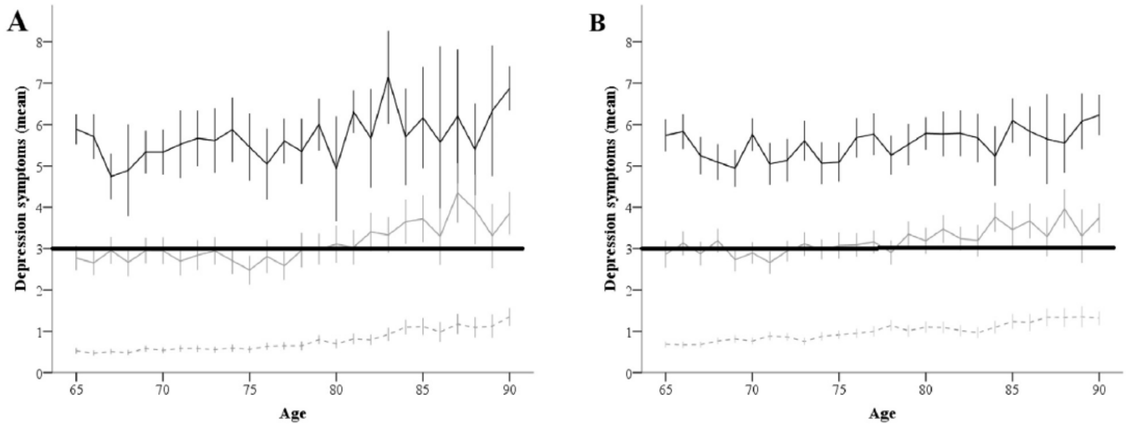
	Multinomial logistic regression (reference category = Class 1)	
	Class 2 (n = 332) RRR (95% CI)	Class 3 (n = 267) RRR (95% CI)
Age	1.03** (1.01, 1.05)	0.86*** (0.84,0.89)
Sex (ref. male)	0.58*** (0.45, 0.74)	0.46*** (0.35, 0.62)
Formal qualification (ref. no)	0.72* (0.56, 0.94)	0.51*** (0.38, 0.68)
Belonging to the 1st-2nd quintile of household wealth (ref. no)	1.77*** (1.36, 2.31)	1.50* (1.10, 2.05)
ADL difficulties (ref. no)	1.46* (1.06, 2.02)	2.30*** (1.61, 3.29)
IADL difficulties (ref. no)	2.80** (1.33, 5.89)	2.77* (1.19, 6.44)
Diabetes (ref. no)	2.03** (1.29, 3.20)	1.86* (1.11, 3.09)
High blood pressure (ref. no)	0.84 (0.65, 1.09)	1.37* (1.03, 1.83)
Physical activity (ref. sedentary)		
Mild	0.60* (0.38, 0.93)	0.59* (0.36, 0.96)
Moderate	0.53** (0.34, 0.82)	0.59* (0.36, 0.94)
Vigorous	0.46** (0.28, 0.76)	0.49* (0.28, 0.84)
CES-D 8 score	1.08* (1.01, 1.17)	1.15*** (1.06, 1.24)

Note: p * < 0.05; ** p < 0.01; *** p < 0.001

4.4. Determinants of mental health: trajectories of depressive symptoms in old age (Study IV)

Three heterogeneous trajectories of depressive symptoms were identified by means of LCMM (see Figure 8). Most participants comprised the normative class (77.35% of men and 68.21% of women, respectively), with slight symptom growth over time (time effect with slope, $\beta = 0.02$, $SE = 0.00$, $p < 0.05$, for both sexes). A subclinical trajectory class featuring increasing levels of symptoms was also found (16.64% of men and 21.25% of women, respectively). Symptoms surpassed the cut-off point of clinical meaningfulness over time in this class (time effect with slope, $\beta = 0.04$, $SE = 0.00$, $p < 0.05$, for men; and $\beta = 0.03$, $SE = 0.00$, $p < 0.05$, for women). A chronic symptom trajectory class was also found (6.01% of men and 10.54% of women), presenting clinically significant symptoms over time.

Figure 8. Depressive symptoms trajectories by class and sex (A = male, B = female).



Note: Thick dark line depicts the cut-off point for clinical meaningful level of symptoms
Dashed grey line=normative trajectory class. Solid grey line=subclinical trajectory class. Solid dark line=chronic symptom trajectory class.

By means of measurement invariance confirmatory models, increasing hearing difficulties and history of psychiatric problems were associated with the chronic symptom trajectory. Subclinical trajectories were associated with lower levels of education, history of psychiatric problems, and increasing visual difficulties. Clinical and subclinical classes presented a worse quality of life and satisfaction with life, as well as more difficulties in ADLs and IADLs, than the normative class.

5. Discussion

Altogether, the compendium of articles composing this thesis provides a series of methodological and statistical approaches for assessing heterogeneous trajectories of functioning and mental health in general population. These approaches allowed for identifying groups of the population with similar aging patterns, using both a global measure of health status, and two core domains of mental health (i.e., cognition and affect). Evidence on the sociodemographic and health related determinants of the aging patters identified is also provided and discussed.

5.1. An approach to identify different patterns of healthy aging

Study I included in this thesis provided evidences of validity for a statistical approach which proved to be useful for assessing and comparing heterogeneous trajectories of healthy aging. On the one hand, this approach allows the estimation of a single common measure of health based on the WHO conceptualization of health (Salomon et al., 2003). Such measure can be used for assessing and comparing health trajectories across epidemiological studies with different design (e.g., number of waves) and measurement characteristics (i.e., different health indicators), thus shedding light into the complex dynamics of health aging. This health measure was sensitive to aging, and presented an adequate ability to predict mortality over ten years in two different samples from the UK and the US populations. On the other hand, the GMM person-centered approach allows to identify groups of the population with similar aging patterns in different domains of functioning (Ram & Grimm, 2009), as well as determinants or factors associated with the health trajectories featured in each group.

Using this approach, Study I of this thesis identified four and five groups of the English and the US populations, respectively, with heterogeneous trajectories of health. A better health status at baseline assessment, as well as higher levels of education and household wealth, were systematically associated with the groups presenting a healthy aging trajectory. On the contrary, the presence of multiple chronic conditions was associated with worse trajectories of functioning across the old age. These results are consistent with previous research evidencing positive links between education, wealth, and health status (Avendano, Jürges, & Mackenbach, 2009; Kahn, Wise, Kennedy, & Kawachi, 2000; McLeod, Lavis, Mustard, & Stoddart, 2003). In that regard, a better education might enhance the understanding of health, facilitating adherence to healthier life-styles. Additionally, it is likely that people with higher education have access to more qualified occupations, which take place in safer environmental contexts, thus reducing exposures to potential risk factors. The positive relationship between wealth and healthy aging might reflect an easier access to better health care systems for high income people (Schöllgen, Huxhold, Schüz, & Tesch-Römer, 2011). Altogether, these results highlight the importance of following a healthy lifestyle in order to reach young older age with a good functional ability. Thus, policy makers should consider the roles of education and wealth as determinants of healthy aging by promoting healthy lifestyles and facilitating effective interventions to all members of society.

5.2. Visual and hearing impairments moderate rates of cognitive decline in old age

In Study II, heterogeneity in normative cognitive aging is addressed by analyzing the moderating roles of visual and hearing functioning impairments on subsequent cognitive decline, providing evidence on the long-term associations of visual and hearing difficulties with cognitive aging in a large representative sample from the UK. This was the first study to use a latent variable approach to model the relationships between visual and hearing difficulties with cognitive decline in a large follow-up of eight years. In that regard, visual and hearing difficulties predicted subsequent cognitive decline, with people presenting either visual, hearing, or both sensory impairments, manifesting a steeper cognitive decline over eight years of follow-up.

Results from Study II are in line with previous research suggesting sensory functioning as moderator of on normative cognitive aging, and thus, support the so called *sensory deprivation hypothesis* (F. R. Lin et al., 2014; Maharani et al., 2018; Yamada et al., 2016). It is shown that people presenting either visual, hearing, or dual sensory impairments, presented an accelerated rate of cognitive decline over 8 years, compared to the control group not presenting any kind of sensory difficulty. This evidence may suggest that visual and hearing difficulties could be considered as early indicators of the neurobiological course of the aging brain. Altogether, results from Study II suggest detrimental long-term effects of impoverished sensory input on cognitive functioning as a result of impairments in visual and hearing systems, highlighting the importance of preserving a good sensory functioning in the old age for potentially slowing down subsequent cognitive decline.

5.3. Determinants of heterogeneous trajectories of sensory-cognitive functioning

Beside the specific unidirectional associations between sensory and cognitive functioning shown in Study II, previous literature has suggested general mechanisms of aging affecting both sensory and cognitive functioning (Lindenberger & Ghisletta, 2009). Such mechanisms would reflect a “common cause” of possibly neurobiological aging, which may jointly deteriorate the common biological substratum of sensory and cognitive systems. In Study III, a latent factor explaining the common variation in visual, hearing, and cognitive functioning remained stable over eight years, suggesting a common etiology for these domains of functioning.

Using self-reported items of visual and hearing functioning, and a set of cognitive tests, a method for developing a cost-effective latent measure of sensory-cognitive functioning is presented in Study III. Evidences of criterion validity were provided for this measure, which presented a good ability to predict dementia ten years later. Similar results have been previously reported, evidencing associations of single measures of visual, hearing, and cognitive impairment with risk of subsequent dementia (Deal et al., 2017; Frank R. Lin et al., 2011; Mitoku, Masaki, Ogata, & Okamoto, 2016). Nonetheless, this was the first time a joint sensory-cognitive measure proved to be useful for predicting pathological forms of cognitive aging.

Using the sensory-cognitive measure, a LCMM-based methodology was applied in order to assess potential heterogeneous trajectories of sensory-cognitive functioning, identifying three population groups with varying trajectories. A modal group comprised of the largest proportion of the sample showed low levels of sensory-cognitive difficulties at baseline, with low-to-moderate increases over time. This group was associated with higher levels of educational attainment and household wealth, as well as physical activity. As discussed in Study I, previous evidence shows a positive association between functional ability, education, wealth, and physical activity (Daskalopoulou et al., 2017; Depp & Jeste, 2006; Kim & Durden, 2007). It is likely that people with higher education have access to more qualified occupations taking place in healthier environments, which may reduce exposure to sensory-cognitive risk factors.

Two additional risk groups were identified by means of GMM, displaying either high levels or accelerated rates of increasing sensory-cognitive difficulties. Both trajectory groups were associated with a common set of risk factors: a worse functional ability, medical-diagnosed diabetes, and depressive symptomatology. These risk factors have already been individually linked to sensory (Brennan, Horowitz, & Su, 2005) and cognitive functioning (F. R. Lin et al., 2014) in previous research. Additionally, high blood pressure and higher levels of depressive symptoms were specifically linked to the group displaying the most accelerated pace of sensory-cognitive difficulties. In that regard, previous studies suggest a common cardiovascular etiology for sensory and cognitive aging (Fischer et al., 2016; Whitson et al., 2018).

5.4. Heterogeneous trajectories of depressive symptoms in the old age

As discussed earlier, the WHO considers affect as a key component of healthy aging (Salomon & Murray, 2004). Previous research has shown that affective disorders, such as depressive symptomatology, are very common and prevalent in the old age (Andreas et al., 2017). However, trajectories of affective dysregulations are far from being unitary or homogeneous among the old population (Hsu, 2012). Study IV identified three heterogeneous trajectories of depressive symptoms in old men and women from a nationally representative sample from the UK. These trajectories corresponded with normative, sub-clinical, and chronic symptom trajectories. Consistent with previous literature (Colman, Ploubidis, Wadsworth, Jones, & Croudace, 2007), a significant difference based on sex was identified in terms of trajectory membership, with a higher proportion of women presenting subclinical and chronic symptom trajectories.

Some health-related factors were identified as determinants of symptom trajectories. As reported in previous literature, history of psychiatric problems was the factor most consistently associated with rising symptom trajectories in both sexes (Carrière et al., 2017). Additionally, increasing visual and hearing difficulties were associated with chronic and subclinical symptom trajectories, respectively. The negative impact of impaired sensory functioning on affect may reflect reward losses due to difficulties in following conversations or in personal autonomy (Tolman et al., 2005). Some of the determinants identified showed sex-specific patterns. For example, the presence of multiple chronic conditions was associated with rising symptom trajectories in women but not in men.

Finally, Study IV shows that heterogeneity in trajectories of depressive symptoms may have negative associations with other healthy aging outcomes. In that regard, compared with the normative trajectory, both subclinical and chronic symptom trajectories presented subsequent lower quality of life and lower life satisfaction. Altogether these results highlight the importance of considering person-specific profiles for clinical diagnosis and treatment selection.

5.5. Strengths

The present thesis has several strengths that should be highlighted. First of all, all studies included in this thesis employ cutting edge statistical methods from two completely different approaches. On the one hand, variable-centered methods, such as SEM, allow for reducing dimensionality among a set of correlated observed variables, and to estimate associations between theoretical constructs (e.g., cognitive function, functional ability, etc.) at a latent level, thus reducing noise in the data. On the other hand, person centered methods, such as GMM, focus on inter-individual differences in intra-individual change, which allows identifying heterogeneity in developmental processes across individuals. Combining both variable and person centered methods proved to be useful for assessing the complex dynamics of aging, allowing identifying population groups with different aging trajectories, and their associated determinants.

Another remarkable strength of this thesis is the use of longitudinal epidemiological studies with large follow-up periods and large nationally representative samples from the UK and the US populations. Although causal inference is limited by the observational design, longitudinal data allows identifying long-term relationships between variables and differential trajectories in relevant health-related outcomes. Moreover, sample representativeness allows some degree of generalization of results to the population where the sample was drawn from.

5.6. Limitations

Some limitations of the studies included in this thesis should be noted. On the one hand, self-reported items were used in all studies, which can be negatively influenced by response style biases (Vaerenbergh & Thomas, 2013). This is particularly relevant in Studies 2 and 3, since the visual and hearing factors were based on self-reports, and not in objective measures of visual and hearing acuity. Further research should be carried out to replicate results from Studies 2 and 3 using objective measures of sensory functioning.

On the other hand, the ELSA and HRS studies are mainly focused on populations aged 50 and over, so evidence on aging patterns in younger cohorts is limited. Future research should be conducted to assess and compare health trajectories and associated determinants across cohorts with different age ranges. This is particularly interesting considering the effect of some healthy aging determinants, such as education, vary across different age groups.

6. Conclusions

Conclusions in English

The following conclusions can be drawn from the four studies comprising this Ph.D. thesis on heterogeneous trajectories of functioning and mental health in general population:

1. Several groups of the English and the US populations presented heterogeneous trajectories of healthy aging trajectories. In both populations, the presence of multiple chronic conditions, the lack of formal qualification, and low levels of household wealth were associated with a worse health trajectory.
2. Regardless the level of cognitive functioning, visual and hearing difficulties are associated with subsequent cognitive difficulties in the old age. Older people presenting visual, hearing or both sensory impairments, had an accelerated rate of cognitive decline.
3. A common latent factor explains a remarkable proportion of visual, hearing, and cognitive difficulties in the old age. Such factor remains stable over a time-span of eight years. Complementing cognitive measures with self-reported items of visual and hearing functioning proved to be useful for enhancing dementia prediction over ten years. Older people with low education and household wealth, more disability, diagnoses of diabetes and high blood pressure, and higher depressive symptoms, presented a steeper decline in sensory-cognitive functioning.
4. Three groups of the older population presenting heterogeneous trajectories of depressive symptoms were identified, representing normative, sub-clinical, and chronic symptom trajectories. History of psychiatric problems, visual and hearing difficulties were associated with chronic and subclinical symptom trajectories, respectively. Subclinical and chronic symptom trajectories predicted subsequent lower quality of life and life satisfaction.

Conclusiones en español

Las siguientes conclusiones pueden ser extraídas de los cuatros estudios comprendidos en esta tesis doctoral sobre trayectorias heterogéneas de funcionamiento y salud mental en población general:

1. Varios grupos de la población Inglesa y Norte Americana presentan trayectorias heterogéneas de envejecimiento. En ambas poblaciones, la presencia de múltiples enfermedades crónicas, la ausencia de educación formal, así como bajos niveles de riqueza en el hogar fueron asociados a una peor trayectoria de salud.
2. Independientemente del nivel de funcionamiento cognitivo, las dificultades visuales y auditivas se asocian a posteriores dificultades cognitivas en la vejez. Las personas mayores que presentan algún tipo de discapacidad visual, auditiva, o ambas, presentan una tasa de declive cognitivo más acelerada.
3. Un factor común explica una proporción destacada de las dificultades visuales, auditivas, y cognitivas en la vejez. Dicho factor permanece estable en un período de ocho años. Complementar medidas cognitivas con ítems auto-informados de funcionamiento auditivo y visual mejora la predicción de demencia a los diez años. Las personas mayores con bajo nivel educativo y de riqueza, con mayores niveles de discapacidad y de sintomatología depresiva, así como con diagnósticos de hipertensión y diabetes, presentan un declive sensorio-cognitivo más acusado.
4. Tres grupos de la población mayor presentan trayectorias heterogéneas de sintomatología depresiva, representando trayectorias normativas, sub-clínica y crónicas de sintomatología depresiva. El historial de problemas psiquiátricos, así como las dificultades visuales y auditivas se asocian a las trayectorias de sintomatología crónica y sub-clínica. Las trayectorias sub-clínica y crónica se asocian con una menor calidad de vida y satisfacción con la vida.

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9. Annex: published manuscripts

Determinants of health trajectories in England and the US: an approach to identify different patterns of healthy aging

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Abstract

Background:

Aging is a multidimensional process with a remarkable inter-individual variability. This study is focused on identifying groups of population with similar aging patterns, and to define the health trajectories of these groups. Socio-demographic and health determinants of these trajectories are also identified.

Methods:

Data from the English Longitudinal Study of Aging (ELSA) and the Health and Retirement Study (HRS) were used. A set of self-reported health items and measured tests were used to generate a latent health metric by means of a Bayesian multilevel IRT model, assessing the ability of the metric to predict mortality. Then, a Growth Mixture Model (GMM) was conducted in each study to identify latent classes and assess health trajectories. Kaplan-Meier survival curves were obtained for each class and a multinomial logistic regression was used to identify determinants of these trajectories.

Results:

The health score generated showed an adequate ability to predict mortality over ten years in ELSA [AUC=0.74; 95% CI=(0.72,0.75)] and HRS [AUC=0.74; 95% CI=(0.73,0.75)]. By means of GMM, four latent classes were identified in ELSA and five in HRS. Chronic conditions, no qualification and low level of household wealth were associated to the classes which showed a higher mortality in both studies.

Conclusion:

The method based on the creation of a common metric of health and the use of GMM to identify similar patterns of aging, allows for the comparison of trajectories of health across longitudinal surveys. Multimorbidity, educational level and household wealth could be considered as determinants associated to these trajectories.

Keywords: health trajectories, healthy aging, longitudinal surveys, health metrics, latent classes.

Introduction

Worldwide life expectancy has considerably increased over the last five decades[1], with an expected increment of people aged 60 or above from 11.2% in 2011 up to a 22% in 2050[2]. However, there are inconsistent findings on whether this increase on the lifespan is accompanied by a better health status[3–5]. There is also a dramatic shift towards increased burden of non-communicable diseases[6]. The World Health Organization's *World Report on Ageing and Health*[7] as a result argues that to get a true sense of the dynamics of aging, the focus should be put on health trajectories in order to optimize well-being and health gains from interventions. Therefore, healthy aging has important implications, since multimorbidity and disability in the elderly population has a remarkable impact in society and economy[8,9].

Aging is a multidimensional process that implies a gradual accumulation of molecular and cellular damage over time, which results in a progressive decline in physical and mental capacities[10], increasing the risk for illness and death[11]. Nonetheless, there are individual differences in the way people age[12,13]. Consequently, developing health metrics to quantify health levels of individuals in a way that could be aggregated to the populations levels is a major challenge in understanding healthy aging trajectories[14].

According to the International Classification of Functioning[15] and the World Health Organization's conceptualization of health status for measurement[14], a measure of health requires quantifying the functional ability of an individual. The definition comprises the individuals' intrinsic capacity and its interactions with their environment. Health status can be measured either through self-reported items capturing the presence of difficulties in a given domain of functioning, or using measured tests of capacity, such as cognitive tasks, walking speed, or grip strength[16,17].

To provide a definition of successful aging is a complex task, as mentioned in a systematic review[18]. Moreover, although health declines with age, individuals do not have identical rates and timing of decline. Adopting a life course approach can help to understand why different people and populations age differently[19–21]. Trajectories on health can have a step-ladder pattern or show a precipitous decline at a determined point in time.

The present study aims at identifying groups of people with varying patterns of health trajectories, their determinants, and socio-demographic patterns associated with those trajectories. A common metric of health, utilizing data from the English Longitudinal Study of Ageing (ELSA)[22] and the Health and Retirement Study (HRS), is used to compare these trajectories[23]..

Methods

Sample and Study design

Data from the first seven waves of the ELSA (2002-2014), and the first eleven waves of the HRS (1992-2012) were used in this paper. Both studies are biannual, longitudinal and focused on adults aged 50 and over, considering nationally representative samples from the English and the US populations, respectively. Specifics of the ELSA sample, study design, and data collection are available at the ELSA project website [https://www.elsa-project.ac.uk/]. All participants in ELSA have given informed consent. Ethical approval for all the ELSA waves was granted from the National Research Ethics Service (MREC/01/2/91). Participants in HRS provided verbal consent to participate and an informed consent document. Collection and production of HRS data was based on the requirements from the University of Michigan's Institutional Review Board (IRB).

Further details of the study design and sampling procedure are available on the HRS website [hrsonline.isr.umich.edu].

Measures

A set of 45 items were initially identified in the ELSA baseline, comprising self-reported health questions related to impairments in body functions, limitations in Activities of Daily Living (ADLs), and limitations in Instrumental Activities of Daily Living (IADLs); and also a set of measured tests covering cognitive functioning and walking speed. A full description of the 45 items is provided elsewhere[17]. Thirty of these 45 items were identified in at least one of the HRS waves and were identified as common items to anchor the scale. The statistical model considered for creating the metric of health allows for the inclusion of the anchoring items as well as the additional items in ELSA but not in HRS. Original questions in ELSA and HRS varied in the number of response categories. Self-reported health questions comprised between two and five response options and some category labels were slightly different in ELSA and HRS. For this reason, a previous harmonization effort was carried out in the present study: after examining the content and potentially different response categories in each question across waves and studies, the original items were coded according to the presence or absence of difficulties (coded as 0 and 1, respectively). For measured tests, the sample was considered separately in each wave of each study and the lower quartile of each distribution determined in each case. Then, the original variable was dichotomized in each wave of each study indicating presence (values lower and equal to the 25th percentile of the distribution, coded 0) and absence (values higher than the 25th percentile of the distribution, coded 1) of difficulties. Higher values in the latent health score obtained from these items indicate a better health status.

Socio-demographic variables as gender, age, formal qualification, ethnicity, and household wealth, were also used in the statistical analysis. Formal qualification was defined in both surveys as having a degree or certificate recognized by the English or the US education system, respectively. Household wealth was measured as the respondent's net value of total wealth (including second home) less all debt. Participants were also asked if a doctor had ever told them that they are suffering from any of the diseases that were included in a list of chronic conditions, and the presence of chronic conditions was categorized in 0, 1, or 2+. Ethnicity was considered only in HRS, since the heterogeneity observed, and comprised four categories: whites, African-American, Hispanic and others. On the other hand, this variable was not included in the specific analyses carried out in ELSA, since the homogeneity of the ELSA sample in terms of ethnicity (the percentage of whites at ELSA baseline was 97.0%).

For mortality in ELSA, data from participants who provided informed consent to linkage to the National Health Service Central Register at baseline were used, and the mortality status was updated at February 2012; while in HRS mortality was determined by matching study records to the National Death Index and using information from the household members participating in the study.

Statistical analysis

A common metric of health was created simultaneously for ELSA and HRS waves, using a Bayesian multilevel Item Response Theory (IRT) method. All parameters were simultaneously estimated using the Markov Chain Monte Carlo approach[24]. Based on the concepts of anchor items and specific-study items, the procedure described in Caballero et al.[17] was employed, considering "study" (HRS/ELSA) as level-variable and transforming the latent score into a 0-100 scale, with higher values indicating a better health status.

Before running the IRT model, the measurement invariance of the 30 common items was tested across both studies. A sequential approach was considered, testing the goodness-of-fit of four nested models which represented respectively configural, metric, strong and strict measurement invariance. A detailed description of the procedure is provided in the Supplementary Material (Appendix 1).

A mixed-effect multilevel regression model was carried out to assess whether the metric is sensitive to aging. Additional details about the statistical approach employed to create the above-mentioned common metric of health and the mixed-effect multilevel regression model, are provided as Supplementary Material (Appendix 1).

The ability of the metric of health to predict mortality over ten years was assessed using Receiver Operating Characteristics (ROC) Curves and adjusting by gender. The mortality analysis was separately carried out for ELSA and HRS, taking health status at 2002 as the predictor in both cases and using the mortality status in 2012 as the outcome. A total of 11,906 participants in ELSA Wave 1 and 12,652 participants in HRS Wave 6, both interviewed in 2002, were considered.

Healthy aging trajectories were then analyzed separately for each study. A Growth Curve Mixture Modeling (GMM)[25] framework was used to identify a finite set of homogeneous groups based on health trajectories across waves in each study. To decide the optimum number of subgroups/classes, the Sample-size Adjusted Bayesian Information Criteria (SABIC), as well as the Lo, Mendell, and Rubin likelihood test (LMR-LRT) were used. The appropriate number of classes to be used in the GMM was based on a Latent Class Growth Analysis (LCGA) model previously implemented. LCGA is a special type of GMM, whereby the variance and covariance estimates for the growth factors within each class are assumed to be fixed to zero. Additional criteria used to select the final model with the corresponding number of classes were: 1) successful convergence; 2) entropy values over 0.70; 3) no less than 1% of total sample in a class; and 4) average of the posterior probabilities of class membership over 0.70. Class membership was based on the highest average of the posterior probability. Growth parameters of each class were estimated, fixing interclass variances of intercepts and slopes to be equal to avoid possible convergence problems.

Based on socio-demographic variables, a multinomial logistic regression analysis was conducted to examine the likelihood of being in each class previously determined in the GMM. In ELSA and HRS, the modal class (the class with the largest sample size) was used as the reference category. In order to conduct a mortality analysis and assess survival rates associated to each class, survival curves by class were generated using Kaplan-Meier estimates. Survival rates across time were considered as the outcome in the Kaplan-Meier curve.

The overall sample (n = 55,684) who participated in any of the waves of ELSA or HRS, was considered in the Bayesian multilevel IRT analysis conducted for creating the common metric of health and the mixed-effect multilevel regression model. All the waves were considered for these analyses. On the other hand, the general profile associated to healthy aging trajectories was assessed considering, in each study, the subset of participants interviewed at baseline (n = 11,906 in ELSA and n = 12,648 in HRS). Data management, descriptive analyses and multilevel models were implemented in Stata[26]. GMM analyses were carried out in Mplus[27], and the *sirt* package[28] in R[29] was employed to conduct the analysis based on the Bayesian multilevel IRT approach.

Results

A total of 55,684 subjects participated in at least one wave of either ELSA or HRS studies. A combined data set was created, with 18,396 participants (54.5% of women) from ELSA and 37,288 participants (56.2% of women) from HRS. In ELSA, a total of 360 subjects from the 11,906 who participated at baseline (3.02%) did not provide informed consent to linkage to the National Health Service Register and were excluded from the mortality analysis. Participants who provided this consent in ELSA were significantly older than those who did not (64.11 ± 10.84 vs. 62.04 ± 10.62; t (11,904) = 3.57; p<0.001), while significant differences between both groups were not found in terms of gender [χ^2 (1) = 2.45; p=0.12] nor formal qualification [χ^2 (1) = 0.50; p=0.48].

A latent score on health was created across the ELSA and HRS data. The Expected-A-Posteriori (EAP) reliability was 0.86. The 30 common items identified showed strict measurement invariance across both studies. Specific details about the measurement invariance are shown in the Supplementary Material (Appendix 1, Table S1). The metric of health was sensitive to aging, as also shown in the Supplementary Material (**Table S2**). The metric showed also an adequate ability to predict mortality in ELSA [AUC = 0.74; 95% CI = (0.72, 0.75)] and HRS [AUC = 0.74; 95% CI = (0.73, 0.75)], with higher scores associated with a lower mortality over 10 years.

Identifying health trajectories in the ELSA study

According to the criteria for determining the number of classes, a four-class GMM was considered for identifying groups of subjects in ELSA based on health trajectories. A modal class was detected (Class 3), comprising a 63% of the total sample. Significant decreasing trends (p < 0.001) in health across time were found for all classes (**Table S3)**. Class 1 showed the strongest decreasing trend, although comprised the smallest proportion of subjects. The general profile at ELSA baseline for each class is showed in **Table 1**.

Considering the modal class as reference, the population was older in the remaining classes as it can be seen in the multinomial logistic regression model (**Table 3)**. When comparing with the modal class, Class 4 (the second largest group) was associated with multimorbidity [OR=1.93; 95% CI=(1.57, 2.38)], less formal qualification [OR=0.78; 95% CI=(0.67, 0.91)] and a lower level of household wealth [OR=1.74; 95% CI=(1.49, 2.03)]. Kaplan-Meier curves associated to classes 1 and 4 showed the highest mortality rates during the follow-up.

Identifying health trajectories in the HRS study

Five classes were identified in HRS. **Table S4** displays the estimated growth parameters for each class. Results revealed a modal class (Class 4), comprising a 57% of the total sample. Decreasing significant trends in health scores across time were found for four out of the five classes. Class 3, which presented the worse health status at baseline (lowest mean intercept), had associated a non-significant (p = 0.115) slope mean. The general profile at HRS baseline is showed in **Table 2** for each class.

In HRS, the modal class (Class 4) was associated with younger people with formal qualification and without chronic conditions, according to the results obtained in the multinomial logistic regression (**Table 3**). When comparing with Class 4 (reference category), multimorbidity was associated with belonging to Class 1 [OR=3.82; 95% CI=(3.33, 4.37)] and specially Class 3 [OR=10.53; 95% CI=(7.60, 14.58)]. In general terms, Class 3, which had the highest percentage of people with chronic conditions, showed the highest rate of mortality. On the other hand, Class 5 (with the highest health score at baseline) showed the highest rates of survival across time.

Discussion

This article provides a methodological approach to identify a finite set of homogeneous population groups based on health trajectories across time. Before assessing health trajectories, a common latent metric of health was jointly estimated using nationally representative samples from the English and US populations. The conceptualization of this health metric is based on intrinsic capacity and functional ability, and summarizes the underlying health status of an individual as an overall latent composite of different domains of human functioning[14]. The metric of health employed in the present article is based on functioning domains as Walking, Sight, Hearing, Balance, Dizziness, Memory, Orientation in time, Cognition, Pain, Energy, Sleep, Incontinence, Mobility, and limitations in ADLs and IADLs[17]. The metric also showed an adequate ability to predict mortality, and it was sensitive to aging, according to the analyses conducted.

The creation of a latent health metric after using information from self-reported items and measured tests, is a procedure which has already been implemented in other researches either to compare health status across studies[16], to compare health status across waves of the same study[17], or to identify relevant factors related to health status within a single study[30–32]. The present article is set in the context of the Ageing Trajectories of Health: Longitudinal Opportunities and Synergies (ATHLOS) project (http://athlosproject.eu/), assessing health trajectories and socio-demographic determinants in longitudinal surveys.

When measuring healthy aging trajectories, the remarkable variability in the aging process between individuals[12] is a key challenge. In that regard, the GMM-based methodology presented in this study allows to: 1) determine a specific number of latent classes that age similarly; and 2) estimate healthy aging trajectories of these groups[25]. This information from class membership could be used to identify factors and determinants of healthy aging trajectories.

According to the results obtained from the multinomial logistic regression model, systematic relationships were detected in terms of health status at baseline, formal qualification, and household wealth across the different classes identified in ELSA and HRS. The modal classes identified in both studies showed a slight decline trend on health across waves and were associated to higher levels of formal qualification and household wealth. These findings are consistent with previous results, where years of education and income were positively related to a better health status[16,33–35]. Education and family income have been also found to be relevant factors to understand the variations in health trajectories when people age[36]. Moreover, our results showed that health status at baseline was strongly related to a better health status across waves in both studies, which highlights the importance of reaching young elderly with a good health status.

The presence of chronic conditions was another factor systematically related to those classes with worse health status and stronger health decline across time in both ELSA and HRS. Specifically, multimorbidity showed a strong association with belonging to those classes, which is consistent with previous results conducted in US[37] and English[17] populations, which revealed a negative association between multimorbidity and health.

Results from the Kaplan-Meier survival curves suggested differences in mortality rates across classes identified in the GMM in both ELSA and HRS studies. Regarding the general socio-demographic profile of the classes with the highest mortality rates in both studies, these classes had lower levels of formal qualification and household wealth. Moreover, they also presented a worse health status at baseline, as well as a higher prevalence of chronic conditions. These findings are consistent with previous results, where years of education and income were positively related to a better health status[33–35].

It is worth noticing that the class with worst health status (i.e., lowest health scores at baseline and accelerated aging decline) in the HRS study comprised the largest proportions of African-American and Hispanic populations. These ethnic differences in aging are consistent with previous research that revealed significant differences in health between whites and non-whites[38–40]. In that regard, some studies suggest that the differences in health between white and non-white populations could be associated with ethnic differences in the use of health care services [41,42].

The method proposed in this paper has been implemented in a dataset comprising two nationally representative samples focused on people aged 50 and over, which allows for generalizing conclusions to other samples of the same populations. Moreover, the methodological approach implemented in this article has two important contributions. Firstly, it allows for the simultaneous estimation of a common health metric for different longitudinal studies, based on a set of self-reported health questions and measured tests that may vary across studies. Secondly, the generated latent health score can be used to identify aging trajectories within each study, which allows for analyzing latent health changes across time in different homogenous groups of the general population.

Some limitations of the present study should be considered. First of all, ELSA and HRS have a different number of waves, and the follow-up time varies between the two studies. Moreover, both studies are mainly focused on population aged 50 and over; although a smaller comparison sample of adults aged 18–49 years has been included in both studies, there is not enough information in relation to younger cohorts. In that regard, further research should be carried out focusing on other population age-groups, especially exploring differences among healthy individuals in their pace of aging[43,44] and considering also that the relationship between education and health declines with age[45]. In addition, the small sample size in some of the latent classes identified by the GMM approach requires caution when interpreting and generalizing results of these trajectories. Other potential limitation could be the presence of a different set of items in both studies

(45 in ELSA, while only 30 of these items were available in some of the HRS waves); however, one of the advantages of the Bayesian multilevel IRT approach considered is that can deal with items varying across studies and waves[17]. In terms of predictive ability, the metric of health obtained has shown a good performance. The use of the approach proposed is especially relevant in the context of the ATHLOS project, where self-reported health items and measured tests can vary across waves and studies.

In conclusion, a methodological approach to assess trajectories of health in longitudinal studies has been proposed in the present article, allowing for the analysis of determinants of these trajectories. A common metric of health was created, allowing for the inclusion of study-specific items. This metric was sensitive to aging and showed a good performance to predict mortality, providing a reliable measure of health and enabling the identification of a finite number of homogeneous classes based on the health scores obtained across the different waves of longitudinal studies. In general terms, the classes with lower health scores at baseline and stronger decline trends on health showed the highest rates on mortality in the English and the US populations. The presence of chronic conditions, the lack of formal qualification, and a low level of household wealth were associated to a worse health trajectory.

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Table 1. Baseline general profile of the four classes identified in the GMM in the ELSA study.

	Class 1	Class 2	Class 3	Class 4	*p*	Effect size
Number of subjects	81	340	7,491	3,994	-	-
Age, Mean (s.d.)	74.59 (11.36)	69.76 (10.19)	60.72 (9.28)	69.58 (10.98)	< 0.001	0.44
Male, n (%)	37 (45.68)	161 (47.35)	3543 (47.30)	1,502 (37.61)	< 0.001	0.09
Mean health score at ELSA baseline (s.d.)	57.88 (10.76)	63.25 (7.68)	65.20 (8.69)	43.78 (8.50)	< 0.001	1.17
Formal qualification, n (%)	48 (59.26)	177 (52.06)	5,133 (68.52)	1,637 (40.99)	< 0.001	0.26
Belonging to the 1st-2nd quintile of household wealth (in Pounds), n (%)	35 (43.21)	151 (44.41)	2,195 (29.30)	2,999 (57.65)	< 0.001	0.27
Number of chronic conditions					< 0.001	0.31
0, n (%)	43 (53.09)	170 (50.00)	4,552 (60.77)	792 (19.83)		
1, n (%)	22 (27.16)	136 (40.00)	2,343 (31.28)	1,772 (44.37)		
2+, n (%)	16 (19.75)	34 (10.00)	596 (7.96)	1,430 (35.80)		

Note: Cramer's *V* was used as effect size measure in the comparisons across categorical variables, while Cohen's *f* was used as effect size measure in the comparisons across continuous variables.

Table 2. Baseline general profile of the five classes identified in the GMM in the HRS study.

	Class 1	Class 2	Class 3	Class 4	Class 5	*p*	Effect size
Number of subjects	3942	116	1,161	7,182	247	-	-
Age, Mean (s.d.)	55.76 (5.59)	58.80 (6.84)	56.24 (5.67)	54.68 (5.58)	57.60 (6.31)	< 0.001	0.13
Male, n (%)	1,552 (39.37)	71 (61.21)	441 (37.98)	6,655 (50.89)	146 (59.11)	< 0.001	0.12
Mean health score at HRS baseline (s.d.)	48.57 (7.80)	56.98 (9.24)	35.10 (8.35)	60.90 (7.97)	62.28 (7.48)	< 0.001	1.05
Formal qualification, n (%)	2,565 (65.07)	71 (61.21)	520 (44.79)	5,927 (82.53)	172 (69.64)	< 0.001	0.27
Belonging to the 1st-2nd quintile of household wealth (in Dollars), n (%)	1,963 (49.80)	67 (57.76)	858 (73.90)	2,082 (28.99)	89 (36.03)	< 0.001	0.29
Ethnicity						< 0.001	0.10
Whites, n (%)	2,685 (68.22)	64 (55.17)	623 (53.75)	5,572 (77.62)	174 (70.45)		
African-American, n (%)	744 (18.90)	31 (26.72)	325 (28.04)	924 (12.87)	43 (17.41)		
Hispanic, n (%)	426 (10.82)	16 (13.79)	182 (15.70)	525 (7.31)	26 (10.53)		
Other, n (%)	81 (2.06)	5 (4.31)	29 (2.50)	158 (2.20)	4 (1.62)		
Number of chronic conditions						< 0.001	0.33
0, n (%)	859 (21.79)	37 (31.90)	74 (6.37)	3,772 (52.52)	113 (45.75)		
1, n (%)	1,373 (34.83)	30 (25.86)	238 (20.50)	2,466 (34.34)	83 (33.60)		
2+, n (%)	1,710 (43.38)	49 (42.24)	849 (73.13)	944 (13.14)	51 (20.65)		

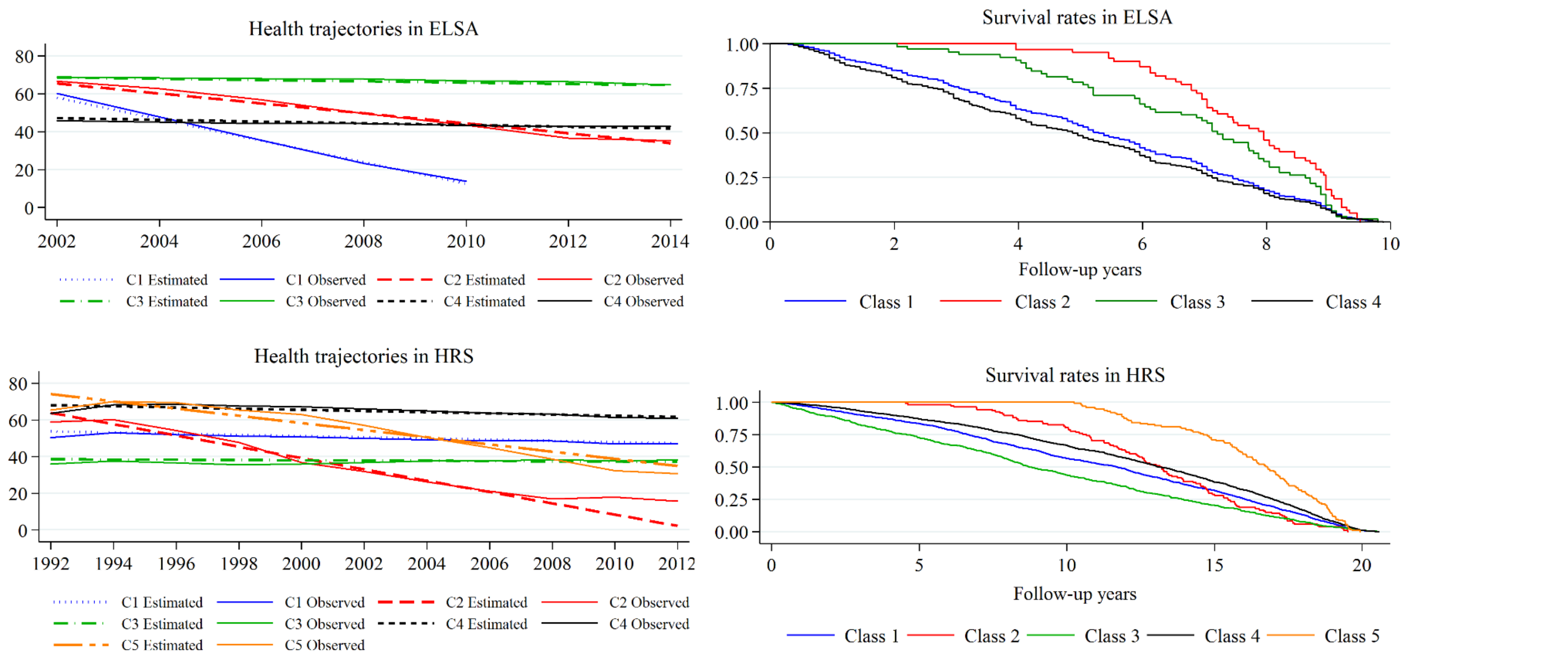
Note: Cramer's *V* was used as effect size measure in the comparisons across categorical variables, while Cohen's *f* was used as effect size measure in the comparisons across continuous variables.

Table 3. Multinomial logistic regression models for predicting classes identified in ELSA and HRS.

	ELSA			HRS			
	Class 1 (n = 81)	Class 2 (n = 340)	Class 4 (n = 3,994)	Class 1 (n = 3,942)	Class 2 (n = 116)	Class 3 (n = 1,161)	Class 5 (n = 247)
Variables	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Age	1.15*** (1.12, 1.18)	1.09*** (1.08, 1.11)	1.07*** (1.06, 1.08)	1.02*** (1.01, 1.03)	1.12*** (1.09, 1.16)	1.02** (1.01, 1.04)	1.10*** (1.07, 1.13)
Health at baseline	0.92 (0.89, 0.95)	1.00 (0.99,1.01)	0.72*** (0.71, 0.73)	0.85*** (0.83, 0.84)	0.95*** (0.93, 0.97)	0.68*** (0.67, 0.69)	1.03** (1.01, 1.04)
Formal qualification (ref. no)	1.49 (0.93, 2.40)	0.85*** (0.67, 0.91)	0.78*** (0.67, 0.91)	0.54*** (0.48,0.62)	0.64* (0.42, 0.97)	0.37*** (0.30, 0.46)	0.61** (0.45, 0.83)
Gender (ref. male)	1.19 (0.76, 1.87)	1.10 (0.88,1.38)	1.21** (1.04, 1.41)	1.21** (1.09, 1.36)	0.89 (0.59, 1.35)	1.33** (1.07, 1.64)	1.08 (0.82, 1.42)
Belonging to the 1st-2nd quintile of household wealth (ref. no)	1.54 (0.97, 2.45)	1.66*** (1.32, 2.10)	1.74*** (1.49, 2.03)	1.73*** (1.55, 1.95)	2.77*** (1.84, 4.17)	2.81*** (2.25, 3.50)	1.30 (0.97, 1.74)
Number of chronic conditions (ref. 0)							
1	0.65 (0.38, 1.11)	1.38** (1.09, 1.76)	1.50*** (1.27, 1.77)	1.73*** (1.53, 1.96)	1.01 (0.62, 1.66)	2.69*** (1.91, 3.80)	1.04 (0.78, 1.40)
2+	1.57 (0.85, 2.90)	1.36 (0.92, 2.02)	1.93*** (1.57, 2.38)	3.82*** (3.33, 4.37)	3.33*** (2.11, 5.24)	10.53*** (7.60, 14.58)	1.51* (1.06, 2.14)
Ethnicity (ref. whites)							
African-American	-	-	-	1.20** (1.04, 1.39)	1.87** (1.17, 2.99)	1.42** (1.10, 1.84)	1.22 (0.85, 1.76)
Hispanic	-	-	-	1.34** (1.10, 1.63)	1.95* (1.07, 3.55)	1.60** (1.16, 2.21)	1.23 (0.78, 1.94)
Other	-	-	-	1.09 (0.76, 1.56)	2.39 (0.92, 6.23)	1.51 (0.79, 2.89)	0.82 (0.30, 2.25)

Full multinomial logistic regression model coefficients in the ELSA (reference category = Class 3; n = 7,491) and HRS (reference comparison category = Class 4, n = 7,182) studies. Ethnicity variable was considered only in the HRS study.

Figure 1. Health trajectories in ELSA and HRS studies, and survival curves by class.



Note: Since the small sample size of people from ELSA Class 1 who continued in the study after the first five waves, health trajectories for this class are shown for the period 2002-2010. The observed trajectories were based on the mean scores on health status observed, while the estimated trajectories were based on the mean values on health status predicted by the GMM model.

Longitudinal Associations of Sensory and Cognitive Functioning: A Structural Equation Modelling approach

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Abstract

Objectives: although visual and hearing impairments have been found to be associated with cognitive decline in the old age, the mechanism underlying this relationship remains unclear. This study aims at assessing the predictive role of visual and hearing difficulties on subsequent cognitive functioning.

Method: 3,508 individuals aged 60 and over from the cohort of the first (2002) and fifth waves (2010) of the English Longitudinal Study of Ageing (ELSA). Five self-reported visual and hearing functioning items were used to assess sensory functioning at baseline. Cognition was assessed eight years later by means of four measured tests covering immediate and delayed recall, verbal fluency, and processing speed. A Multiple Indicators Multiple Causes approach was used to assess the longitudinal associations of visual and hearing functioning with cognitive difficulties. A multi-group longitudinal measurement invariance was used to estimate latent change in cognitive difficulties across groups of participants presenting either visual, hearing, or dual sensory impairment (i.e., those reporting difficulties in both visual and hearing functioning items).

Results: visual (β=0.140, p<0.001) and hearing (β=0.115, p<0.001) difficulties predicted cognitive difficulties eight years later. The latent increase in cognitive difficulties was steeper in people with visual impairment (d= 0.52, p<0.001), hearing impairment (d=0.50, p<0.001), and dual-sensory impairment (d=0.68, p<0.001) than those non-impaired (d=0.12, p<0.001).

Discussion: visual and hearing difficulties were identified as predictors of subsequent cognitive decline in the old age. Interventions to prevent visual and hearing difficulties may have a substantial impact to slow down subsequent age-related cognitive decline.

Key words: vision impairment; hearing impairment; cognition.

Introduction

Aging is a multidimensional process comprising cumulative damages of molecular and cellular structures over time (Beard et al., 2016), resulting in a gradual degradation of several physical and mental capacities. Age-related declines in cognitive and sensory functioning are well documented in the literature (Roberts & Allen, 2016).

Diverse aspects of fluid cognition, such as spatial visualization, inductive reasoning, episodic memory, or processing speed show a significant decline over time (Salthouse, 2004, 2009). Age-related cognitive decline is associated with relevant health-related outcomes, such as disability (Nikolova, Demers, & Béland, 2009; Olaya et al., 2016), mortality (MacDonald, Hultsch, & Dixon, 2011; R. S. Wilson, Segawa, Hizel, Boyle, & Bennett, 2012), or well-being (Robert S. Wilson et al., 2013).

Similarly, visual and hearing functioning also decline with age. In fact, age-related hearing impairment is the most common sensory impairment among the older population (Van Eyken, Van Camp, & Van Laer, 2007), and it is associated with several adverse health-related outcomes, such as depression, social isolation, or loss of self-esteem (Gates & Mills, 2005). Likewise, visual functioning declines with advancing age, yielding adverse changes in different visual processes, like visual acuity (Kaido et al., 2011), motion perception (Hutchinson, Arena, Allen, & Ledgeway, 2012), or temporal resolution of vision (Culham & Kline, 2002). These declines in vision are also associated with important outcomes, such as disability (West et al., 2002) or depressive symptoms (Zheng et al., 2016).

Recent literature reviews summarize a strong body of evidence indicating a link between sensory and cognitive functioning in older adults (Humes & Young, 2016; Roberts & Allen, 2016; Wayne & Johnsrude, 2015). Although the relationship between visual and hearing functioning and cognition in older adults has been shown both cross-sectionally (S. P. Chen, Bhattacharya, & Pershing, 2017; Lindenberger & Baltes, 1994; Ong et al., 2012; Wettstein, Wahl, & Heyl, 2017) and longitudinally (Fischer et al., 2016; F. R. Lin et al., 2014; Frank R Lin et al., 2013; M. Y. Lin et al., 2004; Lindenberger & Ghisletta, 2009; Maharani, Dawes, Nazroo, Tampubolon, & Pendleton, 2018; Yamada et al., 2016), the mechanisms underlying this relationship are not clear yet. Several hypotheses have been proposed to address the sensory-cognitive relationship (Roberts & Allen, 2016). According to the *sensory deprivation hypothesis* there is a causal link between sensory impairment and cognitive dysfunction. Age-related hearing and visual impairments are intricate disorders associated with both environmental and genetical factors (Bourne et al., 2014; Van Eyken et al., 2007). Thus, the quality of the sensory stimuli input is impoverished due to impairments in sensory functioning, which in a long-term would produce neural atrophy in central brain structures, leading to declines in cognitive performance (Baltes & Lindenberger, 1997; Lin et al., 2014; Lin et al., 2004; Lindenberger & Baltes, 1994; Yamada et al., 2016).

Considering the expected increase in the worldwide population aged 60 and over (Bloom et al., 2015), and the important economic burden and health care utilization expenditures of people with mild cognitive impairment (Lin & Neumann, 2013; Ton et al., 2016), it is important to assess the roles of visual and hearing functioning as predictors of subsequent cognitive decline in older population. Thus, this study aims at assessing the longitudinal associations of visual and hearing difficulties with cognitive difficulties in a time-frame of eight years in a nationally representative sample of 3,508 participants aged 60 and over from the English Longitudinal Study of Ageing (ELSA). In addition, change in cognitive difficulties over eight years will be estimated at a latent level and separately for people either with visual, hearing, or dual sensory impairment, as well as for those non-impaired, in order to assess potential differences in cognitive decline according to different types of sensory impairment.

Methods

Sample and study design

The present study comprises a sample of 3,508 participants age 60 and over from the first (2002) and fifth waves (2010) of English Longitudinal Study of Ageing (ELSA) (Steptoe, Breeze, Banks, & Nazroo, 2013). The ELSA is a biannual longitudinal study focused on nationally representative samples of people aged 50 and over from the English population. Participants provided informed consent, and the National Research Ethics Service granted ethical approval for all the ELSA waves (MREC/01/2/91). Further details on the specifics of the ELSA can be found elsewhere [https://www.elsa-project.ac.uk/].

Measures

Visual and hearing functioning.

Visual and hearing functioning were assessed at ELSA baseline (wave 1 - 2002). Visual functioning was assessed by means of three self-reported items covering eyesight in far, near, and general vision. For hearing functioning, self-reported hearing functioning and presence of difficulties following a conversation with background noise were used. These original variables were five-category questions (except self-reported difficulties following a conversation which had two categories), with the following categories in all cases: “Excellent”, “Very good”, “Good”, “Fair” and “Poor”. The full description of these items can be seen in table S1. For both visual and hearing functioning, participants were assessed with their visual and hearing aids if they had them. For the purpose of the present study, these variables were dichotomized, collapsing “Excellent”, “Very good” and “Good” as “Absence of difficulties”. In the dichotomous variable created, values coded as “Fair” and “Poor” were considered as indicators of “Presence of difficulties”.

Cognitive functioning.

Cognitive functioning was assessed both at ELSA baseline (wave 1- 2002) and wave 5 (2010). The assessment of cognitive functioning comprised four measured tests of verbal fluency, processing speed, and short-term and long-term memory (Steptoe et al., 2013). The verbal fluency task consisted in naming the maximum number of animals in one minute. The total score was the number of animals named by the participant. The processing speed score was obtained from a letter cancellation task where participants had to identify and mark two target letters in a page of 65 random letters. Finally, the short-term and long-term memory scores corresponded with the number of words recalled by the participant from a list of ten common words, immediately and after a short delay, respectively. All the scores derived from the cognitive functioning tests were dichotomized using the lower quartile of each distribution as cut-off point for indicating presence of difficulties. Participants were assessed with their visual and hearing aids if they had them.

Other covariates.

Participants also provided information on socio-demographic variables, including age, sex, household wealth, and possessing formal qualification. Household wealth comprised total net non-pension household wealth, including financial, physical, and housing wealth owned by the household minus all debt. Household wealth was dichotomized using the 2nd quintile of its distribution in order to indicate the belonging to the less wealthy groups of the sample. The range of values included in the 1st and 2nd quintiles of household wealth ranged from -22946£ to 95195£. Formal qualification was defined as having any official academic certificate recognized by the English system (from having completed primary school to university degree).

Statistical analysis

Descriptive statistics.

Descriptive statistics of the overall, the analytical, and the drop-out sample were computed. Potential differences in basic sociodemographic data between the analytical and drop-out sample were tested either with chi-square independence tests, or two-sample t-tests. Effect sizes were also computed: Cramer`s V for chi-square tests, and Cohen`s d for t-tests. Cramer's V values of 0.10, 0.30, and 0.50 indicated small, medium and high effect sizes, respectively; in the case of Cohen's d, these cut-off points were 0.20, 0.50 and 0.80, according to Cohen's guidelines (Cohen, 1988) in both cases. Regarding Cohen's d values, they represent the standardized latent change in cognitive difficulties from baseline to wave 5.

Multiple Indicator Multiple Causes Structural Equation Models.

Two Multiple Indicator Multiple Causes (MIMIC) Structural Equation Models to test for *sensory deprivation hypothesis* principles were fitted using Means Adjusted Weighted Least Squares

(WLSM) estimator and tetrachoric correlations. Firstly, a MIMIC solution to model cognitive difficulties at follow-up under the influence of hearing and visual impairment without including the effect of cognition at baseline. A second MIMIC model controlling the effect of cognitive difficulties at baseline was also fitted. In both MIMIC models the exogenous effect of chronological age at baseline was included. The beta parameters reported in these models denote the standardized regression weight of each exogenous ("independent") latent variable predicting the corresponding endogenous ("dependent") latent variable. They can be interpreted as partial correlations, with higher absolute values indicating a stronger association.

Based on the response patterns to the self-reported difficulties, a factor defining visual impairment (VI), hearing impairment (HI), dual sensory impairment (DSI), and non-impairment (NI) was generated. If respondent reported at least 1 difficulty on any item of the visual domain, it was included in the VI group. The HI group included only participants presenting difficulties in general hearing. Those participants presenting at least one difficulty in the visual domain and in general hearing were included in the DSI group. Potential differences in basic socio-economic variables were tested either using one-way analysis of variance (ANOVA) or chi-square independence test. Effect sizes for these comparisons were also obtained, using partial eta-squared for the ANOVA and Cramer`s *V* for the chi-square tests (Cohen, 1988).

Longitudinal and multi-group measurement invariance.

Finally, to assess and compare the extent of cognitive decline across the four groups of sensory impairment at a latent level, it is required to achieve strong measurement invariance across time and groups in the cognitive difficulties latent factor. Thus, three nested measurement models of the cognitive difficulties factor were fitted using Structural Equation Modelling (SEM). Firstly, an unconstrained model comprising two cognitive difficulties factors (at baseline and wave five respectively) with free parameters across time points and groups. Secondly, factor loadings (λ) and thresholds (τ) of the cognitive difficulties factor were constrained to be equal across measurement occasions, but free across groups, in order to assess longitudinal measurement invariance ($\lambda_{11}= \lambda_{12}$, $\lambda_{21}= \lambda_{22}$, $\lambda_{31}= \lambda_{32}$, $\lambda_{41}= \lambda_{42}$, $\tau_{11}= \tau_{12}$, $\tau_{21}= \tau_{22}$, $\tau_{31}= \tau_{32}$, $\tau_{41}= \tau_{42}$). In the common factor model, the lambda parameter represents the factor loading of an item on a specific latent factor (i.e., the direction and magnitude of the lineal relationship between the item / observed indicator and a latent factor). The tau parameter (τ) denotes the threshold of an item, which provides information on the continuous latent response underlying the proportion of individuals endorsing each response category of a categorical item (Wirth & Edwards, 2007). Finally, factor loadings and thresholds were constrained to be equal across time points and groups. This last model assures that the meaning and metric of the cognitive difficulties factor is invariant across groups and occasions, allowing for the estimation of a standardized comparable measure of cognitive change across groups (α_2).

Minimal identification constraints were imposed to identify the longitudinal measurement invariance models (Widaman, Ferrer, & Conger, 2010): 1) the metric of the latent factor at the first measurement occasion was standardized, fixing its mean and variance to 0 and 1, respectively (α_1=0, σ^2_{11}=1); and 2) the first factor loading was freely estimated at the first time-point, whereas it was constrained to be equal at the second measurement occasion ($\lambda_{11}= \lambda_{21}$). In both models, the error terms of the same indicators were allowed to correlate across the two-time points for modelling unique item effects.

The goodness-of-fit of the longitudinal and multi-group measurement invariance models was assessed according to the recommendations proposed in the literature (Hu & Bentler, 1999; Reise, Widaman, & Pugh, 1993): Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) values higher than 0.95, and Root Mean Square Error of Approximation (RMSEA) value lower than 0.08 were considered as indicators of appropriate fit. The longitudinal and multi-group measurement invariance analysis was based on changes in the CFI values lower than 0.01, and on changes in RMSEA values lower than 0.015 across the three different nested models (Chen, 2007).

Results

Descriptive statistics and attrition analysis

Table 1 contains the baseline sociodemographic profile of the overall sample (N=3,508), the analytical sample (n=2,912) and the drop-out sample (n=596), as well as the results of the attrition analysis conducted to assess potential differences between the analytical and drop-out samples. The drop-out sample comprised a 16.99% of the overall sample and were significantly older (p<0.001; Cohen`s d=0.63), with a higher percentage of people belonging to the 1st or 2nd quintile of household wealth (p<0.001; Cramer's V=0.09), and less qualified (p<0.001; Cramer's V=0.08). Nonetheless, these differences were small according to Cohen's guidelines (Cohen´s d < 0.20; Cramer's V < 0.10 for all differences), and therefore, it is assumed that they do not suppose a threat to the representativeness of the sample.

The presence of difficulties in visual functioning was reported by an 8.27%, a 10.13%, and a 13.65% in far, near and general vision, respectively. In the case of hearing functioning, a 37.51%

of the sample had difficulties for following a conversation, while a 21.87% was considered as reporting difficulties in general hearing.

Multiple Indicator Multiple Causes sensory deprivation models

The two sensory deprivation MIMIC models presented an adequate fit (Model 1: [$\chi^2(31)=392.03$, $p<0.001$; CFI=0.96; TLI=0.95; RMSEA=0.055, 90% CI(0.051,0.060)]; Model 2: [$\chi^2(67)=730.42$, $p<0.001$; CFI=0.97; TLI=0.94; RMSEA=0.053, 90% CI(0.050,0.056)]). All the standardized factor loadings of the measurement models were high and statistically significant ($p<0.001$) in the two MIMIC models. Standardized estimates of the MIMIC Model 2 (controlling the effect of cognitive difficulties at baseline) are presented in Figure 1. Standardized factor loadings in MIMIC Model 2 (Figure 1), ranged from 0.845 to 0.943 in the visual difficulties factor, from 0.726 to 0.972 in the hearing difficulties factor, and from 0.369 to 0.878 in the cognitive difficulties factor. Regarding the structural part of the MIMIC models, all the standardized regression weights were also statistically significant ($p<0.001$).

Results from both models revealed significant direct effects of visual (Model 1: $\beta=0.143$; Model 2: $\beta=0.140$) and hearing (Model 1: $\beta=0.114$; Model 2: $\beta=0.115$) difficulties at baseline on cognitive difficulties eight years later. It is important to note that these longitudinal effects of sensory functioning on cognition remain stable even after controlling the effect of cognitive status at baseline (Model 2, Figure 1). In addition, age-related differences in visual (Model 1: $\beta=0.145$; Model 2: $\beta=0.145$), hearing (Model 1: $\beta=0.118$; Model 2: $\beta=0.115$) and cognitive (Model 1: $\beta=0.398$; Model 2: $\beta=0.237$) functioning were found in both models.

Longitudinal and multi-group measurement invariance

The three measurement invariance models presented an adequate fit (Table 2), with CFI and TLI values over 0.95, and RMSEA values below .08. Although a slightly significant increment in CFI was found between models 2 and 3 (ΔCFI=0.016), the increase in RMSEA was non-significant (ΔRMSEA=0.010), and considering all the goodness-of-fit indices of the model it presented a good fit (CFI=0.961; TLI=0.958; RMSEA=0.067). In addition, it should be mentioned that the cut-off point of ΔCFI=0.01 is proposed for the sequential comparison of four levels of measurement invariance across groups with a smaller number of parameter constraints: 1) configural, 2) metric (equal loadings), 3) strong (equal loadings and intercepts), and 4) strict (equal loadings, intercepts, and residual variances). In this case, there was a larger difference in the number of parameters constrained from models two to model three (equal factor loadings and). Therefore, according to model 3 (Figure 2) evidences of strong longitudinal and multi-group strong measurement invariance were found, and based in this model, change in cognition was estimated in each group of sensory impairment, using the standardized latent mean in the cognitive difficulties factor (α_2) as effect size measure.

Table 3 contains a general sociodemographic profile of each group of sensory impairment along with the estimated standardized latent change in cognition. Statistically significant differences in all sociodemographic variables across the groups of impairments were found (p<0.001). Nonetheless, according to Cohen's guidelines the effect sizes associated with these differences were small (partial eta-squared < 0.06; Cramer's $V \sim 0.10$).

The estimated latent cognitive change contained in Table 3 reflects the standardized change in the latent mean of the cognitive difficulties factor from baseline to wave five. This measure is in standard deviation units, with higher values indicating worse cognitive status (i.e., more cognitive difficulties). All groups experienced a significant increase ($p<0.001$) in cognitive difficulties at a latent level. Nonetheless, the change was larger for those with some sensory impairment. More specifically, the steeper increment in cognitive difficulties was found for those either with DSI ($\alpha_2 = 0.68$), VI ($\alpha_2 = 0.52$), or HI ($\alpha_2=0.50$), whereas the non-impaired group presented the smallest increment in cognitive difficulties ($\alpha_2 = 0.12$).

Discussion

In the present study, visual and hearing difficulties were independently associated with a worse cognitive functioning eight years later in a nationally representative sample of older adults from the UK. These longitudinal associations emerged even after controlling for the effect of chronological age and cognitive status at baseline. Regarding cognitive change, subjects presenting difficulties in any sensory domain showed an accelerated rate of cognitive decline, especially those with dual sensory impairment.

Our results support the *sensory deprivation hypothesis* for explaining the link between sensory and cognitive functioning in the older age since visual and hearing difficulties predicted subsequent cognitive decline eight years later. It is important to highlight that these relationships were not due to an advanced age nor a worse cognitive status at baseline, since these effects were controlled in the models. Moreover, unlike previous studies using single measures of cognitive functioning, we modeled the abovementioned relationships at a latent level, thus considering only the common variance shared by a wide set of cognitive measures assessing diverse processes. Although significant, the magnitude of these associations was relatively small, and was slightly higher for the visual than the hearing domain (accounting for 1.96% and 1.32% of the cognitive functioning variance, respectively). These results are consistent with previous cross-sectional and longitudinal studies using either objective sensory measures of threshold sensitivity (Fischer et al., 2016; Lin et al., 2014; Lin et al., 2013; Lin et al., 2004), or self-reported questions of sensory functioning (Liu, Cohen, Fillenbaum, Burchett, & Whitson, 2016; Maharani et al., 2018; Yamada et al., 2016).

It is important to consider results from previous studies addressing alternative hypotheses for explaining the sensory-cognitive relationship in the old age. Lindenberger and Ghisletta (2009) evidenced significant correlations between cognitive, visual and hearing decline, suggesting common age-related mechanisms underlying these domains. However, as pointed out by the authors, these correlations were moderate in magnitude, thus suggesting the need of disentangling general and specific mechanisms of aging. In that regard, our study provides evidence on specific unidirectional long-term mechanisms by which poor sensory functioning impacts on subsequent cognitive decline.

We showed that people manifesting some type of sensory impairment at baseline, regardless the extent of that impairment, manifested a larger decline in cognitive functioning over eight years. The most accelerated rate of cognitive decline was observed in people with presenting difficulties on both visual and hearing domains at baseline. Similarly, a longitudinal study comprising 1,989 nursing home residents showed that the rate of cognitive decline of those with

DSI doubled the rate of those non-impaired (Yamada et al., 2016). Results were similar in another longitudinal study (Lin et al., 2004) comprising 6,112 old women, where individuals with DSI presented the highest odds of cognitive decline. It should be noted that cognitive decline was almost equal for people either with VI or HI. This is not consistent with previous research showing non-significant associations of hearing impairment with worse cognitive status (Lin et al., 2004; Yanan et al., 2018). These discrepancies might be due to the use of general screening tests of cognitive impairment as measures of cognitive functioning, as well as shorter follow-up lengths.

This study has several methodological strengths in comparison with previous research. Firstly, our study comprised a large nationally representative sample of older adults and we conducted an attrition analysis to assess potential differences between the analytical and the drop-out samples, which provides evidence on the generalizability of the results. Secondly, we use a SEM approach to assess the longitudinal relationships between sensory and cognitive functioning, not at an observed but at a latent level (Maharani et al., 2018). This approach is more robust than others implemented in previous studies, since it allows for quantifying changes in a latent factor accounting for the common variance underlying a set of observed cognitive indicators, thus reducing noise in the data. In addition, instead of using a general screening test of dementia as outcome, our cognitive indicators are performance tests assessing specific cognitive processes. Finally, we quantified cognitive change at a latent level using a longitudinal multi-group measurement invariance approach, which guarantees the validity of comparisons across groups of impairments over time.

Some limitations of the study should be noted. On the one hand, the measures of visual and hearing functioning are self-reported and might be influenced by response style biases (Vaerenbergh & Thomas, 2013). Additionally, there were few observed indicators for the hearing domain. On the other hand, the extent of sensory impairment was not considered in the formation of the groups of sensory impairment. In that regard, future research should be conducted to assess the impact of the magnitude of sensory impairment on cognitive functioning. Additionally, further research could be focused on explaining different trajectories of cognition and how these trajectories could be related to trajectories of visual and hearing functioning. Moreover, specific cognitive domains could be assessed in these trajectories, exploring also long-term effects of sensory impairment on specific cognitive domains.

Some clinical implications may be derived from our results. The longitudinal association of impairments in sensory functioning and later cognitive decline suggests that visual and hearing difficulties could be early markers of the neurobiological course of brain while aging. Thus, interventions to prevent or compensate sensory impairments could be promising in slowing down the pace of age-related effects on cognitive domain. In that regard, a recent longitudinal study following 2,040 older adults have shown a positive effects of hearing aid on trajectories of cognitive performance over 18 years (Maharani, Dawes, Nazroo, Tampubolon, & Pendleton, 2018.). To our knowledge, there is no evidence suggesting a positive effect of visual aid use or cataract surgery on cognitive decline (Hall, McGwin Jr., & Owsley, 2005). Further longitudinal studies should be conducted to provide evidence on the potential benefits of visual aids on age-related cognitive decline. In addition, preventive health policies should highlight the importance of maintaining a good sensory functioning in the old age, disseminating the available evidence on the modifiable risk factors of visual (e.g., uncorrected refractive error) and hearing (e.g., noise exposure) impairment (Bourne et al., 2014; Van Eyken et al., 2007).

In conclusion, this study shows that visual and hearing functioning is associated with subsequent cognitive difficulties in the old age. Moreover, sensory-impaired older adults may experience an accelerated rate of cognitive decline than those non-impaired. Thus, visual and hearing difficulties might be used as early indicators of cognitive decline. These findings highlight the importance of preserving a good sensory functioning in the old age, not only for maintaining a good functional status (Liu et al., 2016) and wellbeing (Toyoshima, Martin, Sato, & Poon, 2018), but potentially also to slow down cognitive decline over time.

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Conflict of interests

None reported.

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Table 1. Baseline characteristics of the sample according to participation and nonparticipation in the follow-up assessment.

	Overall sample (*N* = 3508)	Drop-out sample (*n* = 596)	Analytical sample (*n* = 2912)	*p*	Effect size
Age, *M* (*SD*)	69.00 (6.48)	72.51 (7.25)	68.28 (6.07)	< 0.001	0.63
Male, *N* (%)	766 (43.18)	239 (40.10)	1262 (43.34)	0.159	0.02
Belonging to the 1st or 2nd quintile of house-hold wealth, *N* (%)	676 (19.27)	155 (26.01)	521 (17.89)	< 0.001	0.09
Formal qualification, *N* (%)	2014 (57.41)	283 (47.48)	1731 (59.44)	< 0.001	0.08

Note: Cramer's V was used as effect size measure in the comparisons across categorical variables, while Cohen's d was used as effect size measure in the comparisons across continuous variables.

Figure 1. Sensory deprivation MIMIC model 2. Standardized coefficients.

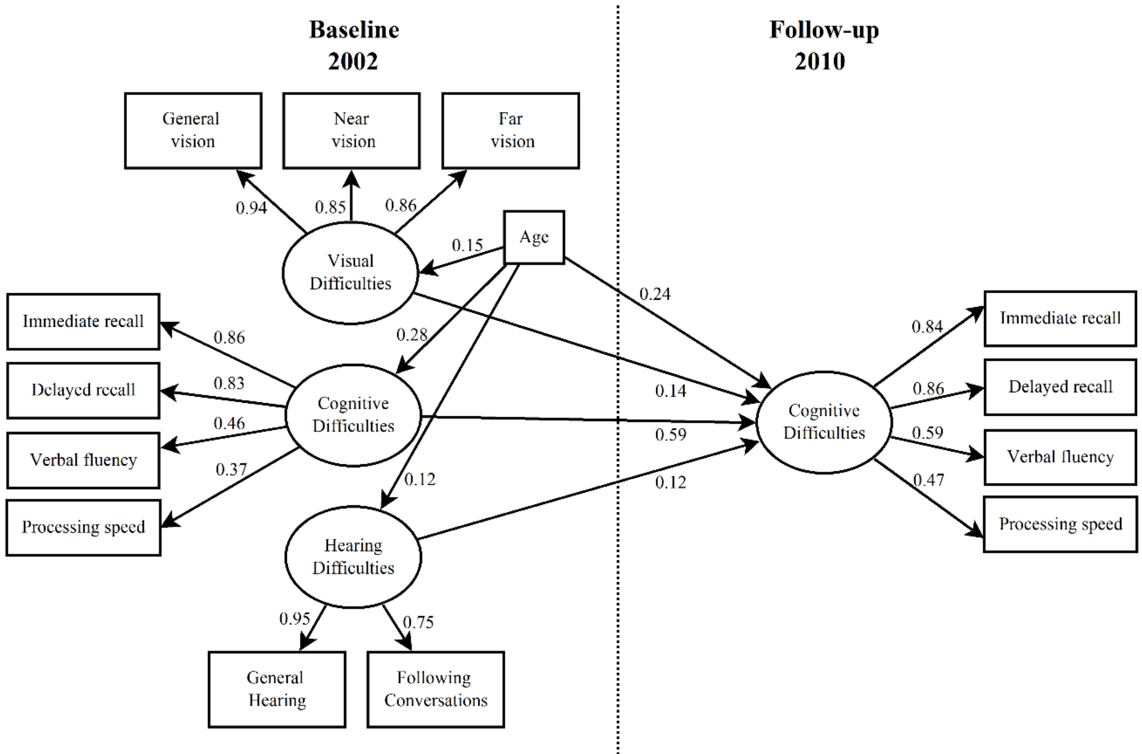

Figure 2. Longitudinal measurement invariance model for estimating latent change in cognitive difficulties.

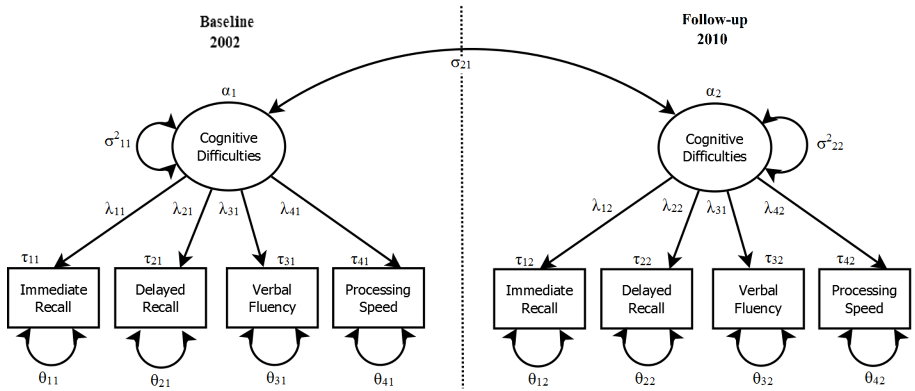

Table 2. Goodness-of-fit indices for the longitudinal and multi-group measurement invariance models.

Model	Parameter constraints	χ^2(df)	CFI	TLI	RMSEA (90% IC)	ΔCFI	ΔRMSEA
1. Unconstrained time and groups	Free parameters between times and groups	315.606*** (58)	0.980	0.961	0.065 (0.058, 0.072)	-	-
2. Longitudinal strong invariance	Equal loadings and thresholds between times, free parameters across groups	361.851*** (84)	0.977	0.969	0.057 (0.051, 0.063)	0.004	0.008
3. Longitudinal and multi-group strong invariance	Equal loadings and thresholds between times, equal loadings and thresholds	513.940*** (105)	0.961	0.958	0.067 (0.061, 0.072)	0.016	0.010

*** $p < 0.001$

CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation. A good model fit is proved by CFI > 0.95, TLI > 0.95, and RMSEA < 0.08.

ΔCFI = absolute difference in CFI across nested model comparisons.

ΔRMSEA = absolute difference in RMSEA across nested model comparisons.

Table 3. Sociodemographic profile and estimated cognitive change from the longitudinal and multi-group strong measurement invariance model by group of sensory impairment.

	VI (*n*=416)	HI (*n*=528)	DSI (*n*=239)	NI (*n*=2325)	*p*	Effect size
Age, *M* (*SD*)	71.04 (7.03)	69.94 (6.48)	71.10 (7.22)	68.20 (6.14)	<0.001	0.04
Male, *N* (%)	120 (28.85)	310 (58.71)	117 (48.95)	954 (41.03)	<0.001	0.16
Belonging to the 1st or 2nd quintile of house-hold wealth, *N* (%)	122 (29.33)	108 (20.45)	77 (32.22)	369 (15.87)	<0.001	0.14
Formal qualification, *N* (%)	182 (43.75)	284 (53.79)	109 (45.61)	1439 (61.89)	<0.001	0.14
Latent cognitive change (*SD*)	0.52 (0.15)	0.50 (0.12)	0.68 (0.17)	0.12 (0.06)		

Note: Cramer's V was used as effect size measure in the comparisons across categorical variables, while partial eta-squared was used as effect size measure in the comparisons across continuous variables.

VI = Visual Impairment; HI = Hearing Impairment; DSI = Dual Sensory Impairment; NI = Non-impaired.

Development of a combined sensory-cognitive measure based on the common cause hypothesis: heterogeneous trajectories and associated risk factors

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Abstract

Background and objectives: there is a link between sensory and cognitive functioning across old age. However, there are no integrative measures for assessing common determinants of sensory-cognitive functioning. This study aims to develop a combined measure of sensory-cognitive functioning, and to identify heterogeneous trajectories and associated risk factors.

Research design and methods: 2,255 individuals aged 60 and over selected from the first six waves (2002-2012) of the English Longitudinal Study of Ageing completed a set of five self-reported visual and hearing functioning items and four cognitive items. Several health-related outcomes were also collected.

Results: the common cause model presented longitudinal factorial invariance [TLI=0.989; CFI=0.991; RMSEA=0.026]. A common factor explained 32%, 36%, and 26% of the visual, hearing, and cognitive difficulties, respectively. The developed sensory-cognitive measure predicted incident dementia over ten years [AUC=0.80; 95% IC=(0.75,0.86)]. A three-trajectory model was proved to fit better, according to growth mixture modeling. Low levels of education and household wealth, disability, diabetes, high blood pressure, depressive symptoms, and low levels of physical activity were risk factors associated with the classes showing trajectories with a steeper increase of sensory-cognitive difficulties.

Discussion and Implications: a time-invariant factor explains both sensory and cognitive functioning over eight years. The sensory-cognitive measure derived from this factor showed a good performance for predicting dementia ten years later. Several easily identifiable socioeconomic and health related risk factors could be used as early markers of subsequent sensory-cognitive decline. Therefore, the proposed latent measure could be useful as a cost-effective indicator of sensory-cognitive functioning.

Keywords: sensory functioning; cognitive functioning; latent classes; Structural Equation Modelling.

Aging is a multidimensional phenomenon associated with declines in both sensory and cognitive functioning. Several cross-sectional and longitudinal studies have evidenced a relationship between sensory and cognitive functioning in the older population (Baltes & Lindenberger, 1997; Humes, Busey, Craig, & Kewley-Port, 2013; F. R. Lin et al., 2013, 2014; M. Y. Lin et al., 2004; Lindenberger & Ghisletta, 2009; Maharani, Dawes, Nazroo, Tampubolon, & Pendleton, 2018; Yamada et al., 2016). Although diverse hypotheses have been proposed to address this link (Humes & Young, 2016; Roberts & Allen, 2016), the causal mechanisms underlying the pattern of relationships between perception and cognition in the older age is still debatable (Whitson et al., 2018).

According to the common cause hypothesis, cognitive and sensory functioning are closely related in older persons since they both depend on the physiological integrity of the brain, which gradually declines in functioning with aging (Roberts & Allen, 2016). Thus, a common neurodegenerative factor simultaneously affecting sensory and cognitive functioning would explain the association between age-related declines in these domains. Neurobiological age-related changes have been found to affect both sensory and cognitive functioning (Chang et al., 2015; Harris & Dubno, 2017). On the other hand, the American Geriatrics Society and the National Institute on Aging highlight that the role of cardiovascular disease and inflammation as common pathways for sensory and cognitive impairment has been overlooked (Whitson et al., 2018). In that regard, a study showed a decrease in the association between sensory impairment and risk of cognitive impairment after controlling for inflammatory and cardiovascular disease and related factors (Fischer et al., 2016). Another recent study showed that visual and olfactory impairments and cardiovascular disease were associated with cumulative incidence of cognitive impairment over 10 years (Schubert et al., 2019). Despite the available evidence, the nature of the common cause and its determinants remain unclear.

Previous research highlights the potential usefulness of developing a combined measure of sensory-cognitive difficulties to explore mechanisms of brain health (Fischer et al., 2016), allowing assessing joint trajectories of sensorineurocognitive functioning across the old age. Moreover, a single measure capturing common aging pathways of sensory and cognitive functioning could be useful for predicting important health-related outcomes, especially those that have been found to be independently associated with these domains of functioning in the older population. For instance, previous research has reported independent associations of visual, hearing, and cognitive impairment with disability (Brennan, Su, & Horowitz, 2006; Cimarolli & Jopp, 2014; Fabbri et al., 2016; Mansbach & Mace, 2018), higher mortality (Gopinath et al., 2013; Wahl et al., 2013; Wilson, Segawa, Hizel, Boyle, & Bennett, 2012), and some mental disorders, like depression (Cosh et al., 2018; Kim, Liu, Cheung, & Ahn, 2018; Lawrence et al., 2019) or dementia (Deal et al., 2017; Lin et al., 2011; Mitoku, Masaki, Ogata, & Okamoto, 2016; Panza, Solfrizzi, & Logroscino, 2015). However, none of these associations have been assessed taking into account the covariance structure underlying sensory and cognitive functioning.

Therefore, the present study had three aims. First, to assess the longitudinal invariance of a common factor accounting for the shared variance among visual, hearing, and cognitive difficulties in older population. It is important to note that although the actual common cause remains unknown, we propose a common cause model that would present factorial invariance over time. Secondly, we aim at developing a latent measure capturing the common variation underlying a set of individual hearing, visual and cognitive functioning measures, assessing its ability to predict incident dementia. Thirdly, to identify groups presenting heterogeneous trajectories of sensory-cognitive difficulties, and their associated risk factors.

Methods

Sample and Study Design

The sample comprised 2,255 participants aged 60 and over from the first six waves (2002-2012) of the English Longitudinal Study on Ageing (ELSA) who had responded to all the self-reported items of sensory functioning and the measured test of cognition. ELSA is a biannual longitudinal study focused on nationally representative samples of people aged 50 and over from the English population (Steptoe, Breeze, Banks, & Nazroo, 2013). All participants provided informed consent. The National Research Ethics Service granted ethical approval for all the ELSA waves (MREC/01/2/91). Further details on the specifics of ELSA can be found in the study website (https://www.elsa-project.ac.uk/).

Measures

Self-reported sensory functioning scale items and cognitive measures employed for the measurement models are shown in Table 1. Visual functioning was measured by means of three self-reported items assessing eyesight in far, near, and general vision. For hearing functioning, self-reported hearing functioning and presence of difficulties following a conversation with background noise were used. These original variables were five-category questions (except self-reported difficulties following a conversation which had two categories), with the following categories: “Excellent”, “Very good”, “Good”, “Fair”, and “Poor”. For both visual and hearing functioning, participants were assessed with their visual and hearing aids if they had them. These items were highly skewed, with a great amount of responses grouped in the ‘best functioning’ categories. In these cases, dichotomizing the values is a habitual strategy (De La Fuente et al., 2018). Thus, these variables were dichotomized, collapsing “Excellent”, “Very good”, and “Good” as “Absence of difficulties”, and “Fair” and “Poor” as indicators of “Presence of difficulties”.

The assessment of cognitive functioning comprised four measured tests of verbal fluency, processing speed, and immediate and delayed recall. The verbal fluency task consisted in naming the maximum number of animals in one minute. The total score was the number of animals named by the participant. The processing speed score was obtained from a letter cancellation task where participants had to identify and mark two target letters in a page of 65 random letters. Finally, the immediate and delayed recall memory scores corresponded with the number of words recalled by the participant from a list of ten common words, immediately and after a short delay, respectively. All the scores derived from the cognitive functioning tests were dichotomized using the lower quartile of each distribution as cut-off point for indicating presence of difficulties.

Participants also provided information on socio-demographic variables, including age, sex, household wealth (net value of total wealth minus all debts), and formal qualification (having an academic certificate recognized by the English educational system). Level of physical activity was obtained by means of a self-reported item comprising four categories: “Sedentary”, “Mild”, “Moderate”, and “Vigorous”. Self-reported doctor-diagnosed diabetes and high blood pressure were also used.

Incident dementia in wave 6 of the ELSA study was obtained following the three-way protocol described by Davies (2017). Participants with either: 1) a physician diagnosis of dementia, 2) a score of 3.5 or higher in the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), or 3) receiving prescriptions for N-methyl-D-aspartate receptor antagonists, anticholinesterase inhibitors, or other anti-dementia medications (such as galantamine, rivastigmine, memantine, donepezil, or tacrine) were categorized as presenting incident dementia if they did not present any of these characteristics in previous waves of the study.

Participants indicated the presence of difficulties to perform six activities of daily living – ADL (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) and six instrumental activities of daily living index – IADL (Graf, 2008). The original variables for assessing ADL and IADL, ranged from 0 (no difficulties) to 6 (difficulties with all six activities of ADL / IADL).

The overall score of the Center for Epidemiologic Studies Depression Scale, 8-item version survey was used to assess the presence of depressive symptoms (CES-D 8) (Turvey, Wallace, & Herzog, 1999). This instrument is made up of eight items with a dichotomous (yes/no) scale of response.

Statistical Analysis

A Structural Equation Modeling (SEM) approach was used to assess the longitudinal factorial invariance of the common cause model proposed in Figure 1 across the first five waves of ELSA. In each wave, this model comprises a second-order latent factor explaining the common variance of the visual, hearing and cognitive difficulties first-order factors. Two nested models were compared in terms of goodness-of-fit. An unconstrained model with free parameters across waves was first implemented to test configural invariance. Then, a constrained model with equal factor loadings and thresholds across waves was used to assess strong factorial invariance. Based on Widaman, Ferrer and Conger (2010), the following constraints were imposed to identify the SEM models: 1) latent factors were standardized at baseline (M=0, SD=1); 2) the factor loading and threshold of the first indicator of each factor were freely estimated at baseline and constrained to be equal at subsequent waves. The residual variances of the same indicators were allowed to correlate across waves for modelling unique item effects. The goodness-of-fit of the SEM models was assessed using the cut-off points proposed by Hu and Bentler (1999); a model showed a good fit when Comparative Fit Index (CFI) and Tucker-Lewis index (TLI) values were greater than .95, and Root Mean Square Error of Approximation (RMSEA) values were lower than .05. The longitudinal factorial invariance analysis was based on a change in the CFI value lower than .01 between the nested models (Cheung & Rensvold, 2002). Means Adjusted Weighted Least Squares (WLSM) estimator for categorical data was used for the SEM models.

If strong factorial invariance was achieved, latent scores on the second-order common factor in each wave were predicted using the factor score regression method. To improve interpretability, these latent scores were then transformed into a 0-100 scale, where higher values indicated higher sensory-cognitive difficulties. The ability of the metric to predict incident dementia ten years later was assessed by means of Receiver Operating Characteristics (ROC) curves, and the Area Under the ROC Curve (AUC). As a sensitivity analysis, we compared the ROC curves and AUCs for predicting incident dementia of the common cause metric with latent scores of visual, hearing, and cognitive functioning estimated separately. AUC values range from .5 (representing no predictive ability) to 1 (representing perfect predictive ability).

Finally, a latent class mixed model (LCMM) (Proust-Lima, Philipps, & Liquet, 2017) was conducted to identify a finite set of groups of subjects with similar sensory-cognitive trajectories. Models with increasing number of latent classes were fitted, considering age effects up to the cubic. The model with lower sample-size adjusted Bayesian information criterion (SABIC) was selected. As additional criteria for selecting the final model, a successful convergence, average of posterior probabilities over .70, and no less than a 5% of the overall sample in each class were considered. The highest average of the posterior probability was used for assigning class membership. A general profile of each class, comprising socio-demographic and clinical information, was obtained. One-way analyses of variance (ANOVAs) and chi-square tests were conducted to assess between-class differences in these variables. Finally, a multinomial logistic regression was conducted to identify determinants of the sensory-cognitive difficulties trajectories.

SEM analyses were conducted with the *lavaan* R package (Rosseel, 2012). Latent class mixed models were implemented with the *lcmm* R package (Proust-Lima et al., 2017). ROC curves, linear, and multinomial regressions were conducted with STATA (StataCorp, 2015).

Results

The mean age of the sample at baseline (N=2,555) was 68.19 years (SD=6.01), with 56.81% of them being women.

Longitudinal Factorial Invariance of the Common Cause Model

The unconstrained model for testing configural factorial invariance [$\chi^2(838)=2252.55$, $p<.001$; RMSEA=.024; TLI=.989; CFI=.991], and the constrained model assessing strong factorial invariance [$\chi^2(883)=2254.90$, $p<.001$; RMSEA=.026; TLI=.989; CFI=.991] presented an adequate fit. Longitudinal factorial invariance of the common cause model was achieved, since the difference in fit between the constrained and unconstrained models was below the cut-off point (ΔCFI < .001).

All items presented significant loadings across waves ($p<.001$) on the hearing difficulties (ranging from .75 to .96), visual difficulties (ranging from .83 to .98) and cognitive difficulties (ranging from .50 to .82) first order factors in the constrained model. The loadings of the visual, hearing, and cognitive difficulties first-order factors on the common cause second order factor were all statistically significant (.57, .60, and .51; $p<.001$). The common cause accounted for 32%, 36%, and 26% of the visual, hearing, and cognitive difficulties factors variance, respectively.

Creation of a Sensory-Cognitive Difficulties Latent Score

The strong factorial invariance common cause model was used to estimate a sensory-cognitive difficulties latent score in each wave. The following means were obtained for the sensory-cognitive difficulties score after rescaling (ranging from 0 to 100): Wave 1: M=31.71, SD=15.87; Wave 2: M=32.34, SD=16.82; Wave 3: M=36.78, SD=16.21; Wave 4: M=40.14, SD=17.16; Wave 5: M=45.20, SD=16.24). According to the results from the ROC curves analyses, this metric at baseline presented a good ability to predict incident dementia at wave 6 [AUC=.80; 95% IC=(.75,.86)]. Results from the sensitivity analysis indicated that latent scores on visual and hearing difficulties factors presented a poor ability to predict dementia over ten years [Visual difficulties: AUC=0.53; 95% IC=(0.41, 0.65); Hearing difficulties: AUC=0.50; 95% IC=(0.37,0.63)]. On the other hand, latent scores on cognitive difficulties presented an appropriate ability to predict incident dementia [AUC=0.70; 95% IC=(0.60,0.80)].

Trajectories of the Common Cause Metric

Results from the LCMM indicated that the model comprising three latent classes with quadratic fixed and random effects presented the lowest SABIC value (SABIC=67237.59). In addition, average of posterior probabilities of class membership were over .70 in every class, with no class comprising less than a 5% of the overall sample. Table S1 contains the sample size and growth parameters of each class. A modal class comprising a 73.44% of the sample (Class 1) was identified. This class presented the lowest sensory-cognitive difficulties at baseline (Intercept = 11.88, p<.001), and a significant slope with both linear (β=1.27, p<.001) and quadratic (β=0.02, p<.001) shape. A class presenting a stable trajectory of high sensory-cognitive difficulties was also identified (Class 2). Although this trajectory class presented the highest levels of sensory-cognitive difficulties at baseline (Intercept = 39.29, p<.001), it only showed a small but significant quadratic shape (β=0.02, $p<.001$). Finally, a sensory-cognitive risk trajectory class was detected (Class 3). This class presented the highest linear slope (β=1.55, $p<.001$). Figure 2 displays the observed sensory-cognitive difficulties trajectories for each class.

The overall profile of the Classes identified in the LCMM is presented in **Table 2**. Results from multinomial logistic regressions conducted to assess baseline determinants of Class membership are presented in **Table 3**. Considering the modal class (Class 1) as reference, classes 2 and 3 comprised more female participants, and were associated with lower levels of education and wealth, as well as a greater presence of ADL and IADL difficulties, self-reported medical diagnoses of diabetes, lower levels of physical activity, and higher CESD score. On the other hand, whereas Class 2 presented older participants compared with the modal class, individuals comprising Class 3 were more likely to be younger. In addition, Class 3 presented a significantly higher proportion of people with high blood pressure.

Discussion

This study presents a methodological approach for developing a combined measure of sensory-cognitive difficulties based on self-reported items of visual and hearing functioning, and a set of cognitive tests. To develop this measure, we proposed a common cause model, testing the temporal stability of a common factor accounting for the observed associations between sensory and cognitive functioning, using a sophisticated SEM approach. This measure presented a good ability to predict incident dementia ten years later. Moreover, we identified three population groups with heterogeneous trajectories of sensory-cognitive difficulties, as well as risk factors associated with groups presenting high or increasing levels of sensory-cognitive difficulties over time.

We identified a latent factor accounting for the common variance between visual, hearing, and cognitive difficulties over eight years. Moreover, the explanatory power of this factor as a predictor of sensory and cognitive functioning remains stable over time, accounting for 32%, 36%, and 26% of the visual, hearing, and cognitive difficulties. These results are consistent with previous research evidencing a common etiology underlying both sensory and cognitive age-related decline (Anstey, Luszcz, & Sanchez, 2001; Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994; Lindenberger & Ghisletta, 2009).

We presented a method for developing a latent measure of sensory-cognitive difficulties based on self-reported items of visual and hearing functioning, as well as a set of cognitive measured tests. Based on the proposed common cause model, this metric allows capturing individual variations in a common factor predicting both sensory and cognitive declines. As suggested previously, this factor might be reflecting senescent neurodegenerative processes affecting perceptive and cognitive functioning, in which people vary in terms of level and rate of decline (Lindenberger & Baltes, 1994; Lindenberger & Ghisletta, 2009). The estimated measure of sensory-cognitive difficulties presented an appropriate ability to predict incident dementia over ten years. It is important to highlight that the common cause explained sensory and cognitive difficulties to a similar extent, and thus, was not overlooking any domain. The abovementioned evidences of criterion validity regarding the metric are in line with previous literature showing isolated associations of visual, hearing and cognitive impairment with risk of dementia (Deal et al., 2017; F.R. Lin et al., 2011; Luo et al., 2018; Mitoku et al., 2016; Panza et al., 2015).

The LCMM-based methodology implemented in this study allowed assessing heterogeneous trajectories of sensory-cognitive difficulties. In that regard, we identified three populations groups with varying trajectories. The modal class comprising the largest proportion of the sample presented low levels of sensory-cognitive difficulties at baseline and a moderate increase over time. This class was associated with higher levels of education, household wealth, and physical activity. These results are consistent with previous literature evidencing positive links between health status and education, income, and physical activity (De La Fuente et al., 2018). In that regard, higher education could enable people to access more qualified occupations which take place in healthier environments, thus reducing exposure to sensory-related risk factors. Similarly, a higher income might facilitate access to better healthcare services and healthy habits.

Two risk groups presenting trajectories with high levels or increases of sensory-cognitive difficulties were identified. A set of common risk factors were associated with these groups: a worse functional ability, medical-diagnose of diabetes, and depressive symptomatology. It is important to highlight that disability and depression have been previously associated with both sensory (Brennan et al., 2006; Cimarolli & Jopp, 2014; Fabbri et al., 2016; Nikolova, Demers, & Béland, 2009) and cognitive functioning (Cosh et al., 2018; Kim et al., 2018). Specific risk factors associated with the group presenting the most accelerated rates of sensory-cognitive difficulties should be noted. This group comprised younger participants, and it was associated with high blood pressure, as well as higher levels of depressive symptoms. These results are in line with previous literature suggesting that the common cause might reflect cardio-vascular related factors affecting both sensory and cognitive functioning (Fischer et al., 2016). Similarly, depression has been associated with both sensory (Cosh et al., 2018) and cognitive functioning (Kim et al., 2018).

Two major limitations of the study should be considered. Firstly, our sample is focused on participants from the UK population aged 60 and over that had responded to all the sensory and cognitive items. Thus, participants who did not survive the time frame considered were excluded from the analyses, constraining the sample and limiting the generalizability of the results. Secondly, the visual and hearing domains were assessed by means of self-reported items, which can be affected by response biases, and may underestimate sensory impairment in older population

(Kamil, Genther, & Lin, 2015). The underestimation of sensory impairment might reduce variability in the responses to self-reports, attenuating the relationships between the sensory and cognitive domains. Subsequently, this attenuation might have a negative impact on the reliability and strength of the common cause factor. Therefore, the predictive ability of the common cause latent measure on incident dementia could be increased in case objective measures of sensory functioning are included in the structural model. Nonetheless, both self-reported measures of visual and hearing impairments present a high correspondence with objective measures of visual (Whillans & Nazroo, 2014) and hearing (Sindhusake et al., 2001) functioning. That aside, the hearing domain only comprised two indicators. Further research should be conducted to assess the temporal stability of the common cause in other populations (e.g., younger cohorts, or populations exposed to sensory or cognitive environmental risk factors), as well as the psychometric properties of the sensory-cognitive measure proposed in this study. Additionally, interdisciplinary research could be useful for identifying other potential neurobiological and genetic markers of the common cause. Neuroimaging studies could help localizing structural and functional regions of interest in the brain associated with both sensory and cognitive functioning. Such findings would be potentially valuable for identifying common neurodegenerative factors associated with declines in both sensory and cognitive functioning. Genome-wide association studies could also help identifying single-nucleotide polymorphisms and genetic correlations across these domains of functioning.

In conclusion, the longitudinal factorial invariance of a common factor accounting for the observed associations between sensory and cognitive functioning is assessed to derive a sensory-cognitive measure from the model. Our results identify a latent factor accounting for the communalities among visual, hearing, and cognitive functioning. Moreover, here we show that the predictive ability of this common factor in relation to sensory and cognitive functioning remains stable over eight years. The sensory-cognitive measure derived from this factor outperformed both sensory and cognitive functioning isolated measures at predicting dementia over ten years. Therefore, complementing cognitive measures with a few self-reported indicators of sensory functioning proved to be useful for enhancing the assessment of risk of dementia. Three population-based groups with different trajectories of sensory-cognitive difficulties were identified. This study suggests that older people with lower education and household wealth, more disability, higher presence of diabetes, high blood pressure, and depressive symptoms, as well as lower levels of physical activity, may present a steeper decline in sensory-cognitive functioning over time, as well as a higher risk of dementia. Considering our results, the proposed measure could be useful as a cost-effective indicator of sensory-cognitive functioning among older population.

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Conflict of interests

None reported.

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Table 1.

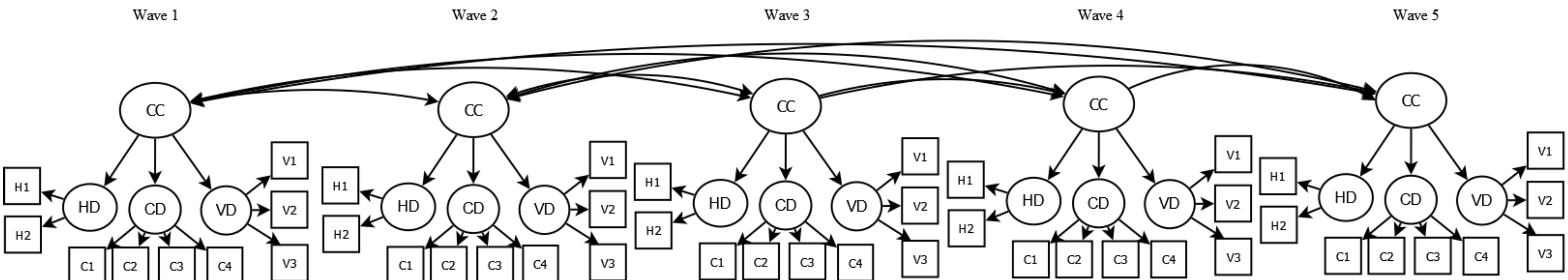
Self-reported sensory functioning scale items and cognitive measures employed for the measurement models.

Vision		Excellent	Very good	Good	Fair	Poor
Far vision	How good is your eyesight for seeing things at a distance, like recognising a friend across the street (using glasses or corrective lens as usual)?	1	2	3	4	5
Near vision	How good is your eyesight for seeing things up close, like reading ordinary newspaper print (using glasses or corrective lens as usual)?	1	2	3	4	5
General vision	How is your eyesight (using glasses or corrective lens as usual)?	1	2	3	4	5
Hearing		**Excellent**	**Very good**	**Good**	**Fair**	**Poor**
General hearing	How is your hearing (using a hearing aid as usual)	1	2	3	4	5
Following conversations	Do you find it difficult to follow a conversation if there is background noise, such as TV, radio or children playing (using a hearing aid as usual)?	No 0	Yes 1			
Cognition*						
Verbal fluency	Participants are asked to name the maximum number of animals in one minute. The total score was the number of animals named by the participant.					
Processing speed	Score obtained from a letter cancellation task where participants had to identify and mark two target letters (P and W) in a page of 65 random letters set out in rows and columns within one minute.					
Immediate recall and delayed recall	Number of words recalled by the participant from a list of ten common words. Word recall is tested immediately and after a short delay filled with other cognitive tests					

**Note:* all cognitive measures are freely available in: https://www.elsa-project.ac.uk/uploads/elsa/docs_w1/booklet.pdf

Figure 1.

Common cause model for explaining the relationships between hearing, visual, and cognitive difficulties.



Note: CC = Common cause; HD = Hearing Difficulties; CD = Cognitive difficulties; VD = Visual Difficulties.

Figure 2.

Trajectories of the combined sensory-cognitive difficulties latent score by class.

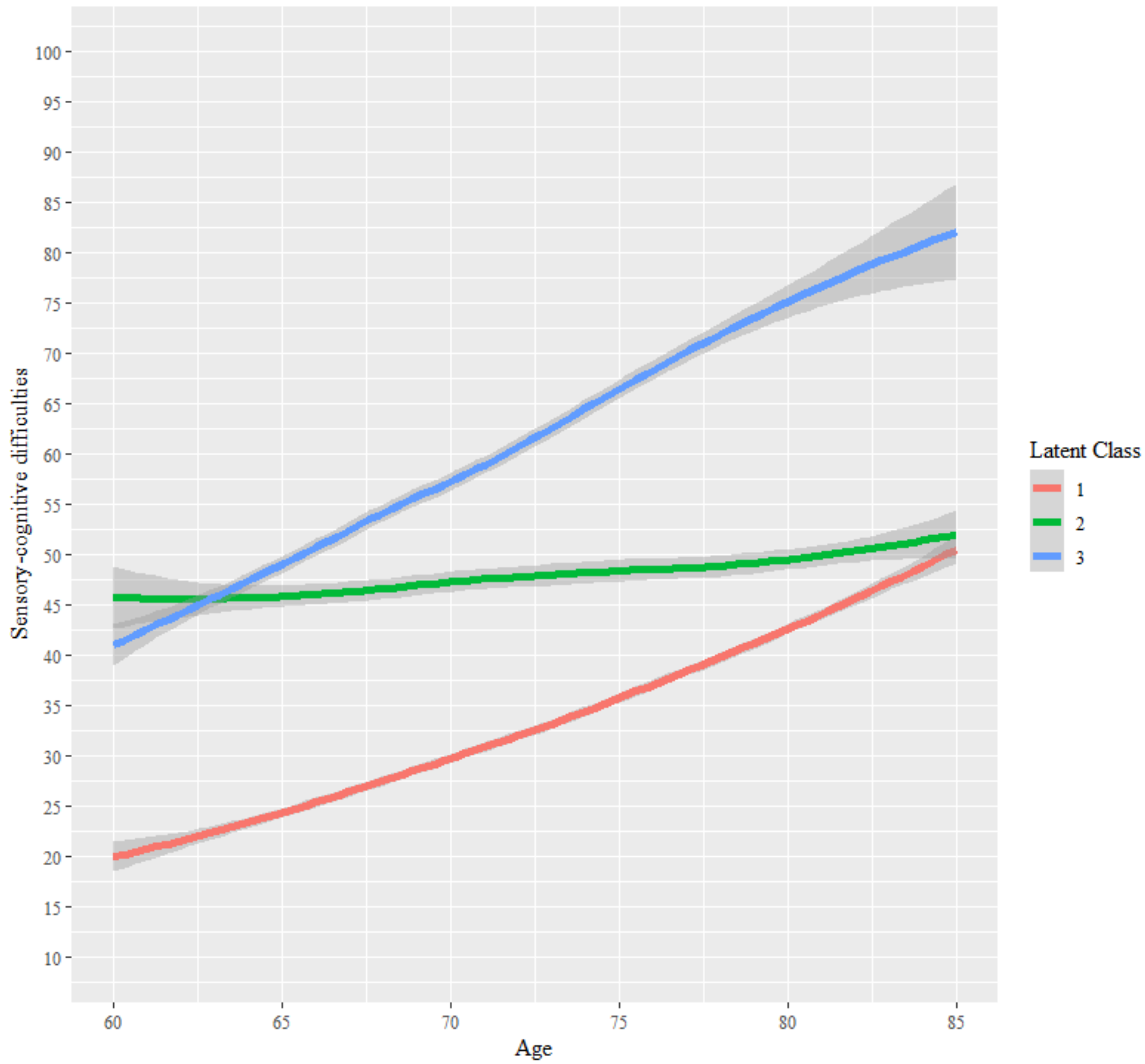


Table 2.

Baseline general profile of the three classes identified in the LCMM.

	Class 1 (n = 1656)	Class 2 (n = 332)	Class 3 (n = 267)
Age, M (SD)	68.36 (5.97)	69.87 (6.48)	65.11 (4.24)
Male, N (%)	668 (40.34)	164 (49.40)	142 (53.18)
Formal qualification, N (%)	1075 (64.92)	172 (51.81)	129 (48.31)
Belonging to the 1st-2nd quintile of household wealth, N (%)	428 (25.85)	144 (43.37)	113 (42.32)
Difficulties in ADL, N (%)	220 (13.29)	86 (25.90)	82 (30.71)
Difficulties in IADL, N (%)	17 (1.03)	15 (4.52)	13 (4.87)
Diabetes, N (%)	72 (4.35)	33 (9.94)	28 (10.49)
High blood pressure, N (%)	620 (37.44)	128 (38.55)	122 (45.69)
Physical activity, N (%)			
Sedentary	90 (5.43)	43 (12.95)	39 (14.61)
Mild	406 (24.52)	99 (29.82)	74 (27.72)
Moderate	817 (49.34)	142 (42.77)	113 (42.32)
Vigorous	343 (20.71)	48 (14.46)	41 (15.36)
CESD score, M (SD)	1.11 (1.60)	1.59 (1.91)	1.83 (2.02)

Table 3.

Multinomial logistic regression model for predicting sensory-cognitive classes identified in the LCMM.

	Multinomial logistic regression (reference category = Class 1)	
	Class 2 (n = 332) RRR (95% CI)	Class 3 (n = 267) RRR (95% CI)
Age	1.03** (1.01, 1.05)	0.86*** (0.84,0.89)
Sex (ref. male)	0.58*** (0.45, 0.74)	0.46*** (0.35, 0.62)
Formal qualification (ref. no)	0.72* (0.56, 0.94)	0.51*** (0.38, 0.68)
Belonging to the 1st-2nd quintile of household wealth (ref. no)	1.77*** (1.36, 2.31)	1.50* (1.10, 2.05)
ADL difficulties (ref. no)	1.46* (1.06, 2.02)	2.30*** (1.61, 3.29)
IADL difficulties (ref. no)	2.80** (1.33, 5.89)	2.77* (1.19, 6.44)
Diabetes (ref. no)	2.03** (1.29, 3.20)	1.86* (1.11, 3.09)
High blood pressure (ref. no)	0.84 (0.65, 1.09)	1.37* (1.03, 1.83)
Physical activity (ref. sedentary)		
Mild	0.60* (0.38, 0.93)	0.59* (0.36, 0.96)
Moderate	0.53** (0.34, 0.82)	0.59* (0.36, 0.94)
Vigorous	0.46** (0.28, 0.76)	0.49* (0.28, 0.84)
CES-D 8 score	1.08* (1.01, 1.17)	1.15*** (1.06, 1.24)

Note: p * < 0.05; ** *p* < 0.01; *** *p* < 0.001

Table S1.

Latent class mixed model estimates for the five-class model.

	Class 1	Class 2	Class 3
N (%)	1656 (73.44)	332.00 (14.72)	267.00 (11.84)
Average probability of class membership	0.89	0.77	0.70
Fixed effects			
Intercept (SE.)	11.88 (0.61)	39.29 (1.52)	34.50 (1.59)
Linear time effect (SE)	1.27*** (0.05)	0.24 (0.18)	1.55*** (0.26)
Quadratic time effect (SE)	0.02*** (<0.001)	0.02*** (<0.001)	0.01 (0.01)
Random effects			
Intercept variance		99.24***	
Linear time effect variance		0.15*	
Quadratic time effect variance		< 0.001	

Note: p * < 0.05; ** p < 0.01; *** p < 0.001

Long-term trajectories of depressive symptoms in old age: relationships with sociodemographic and health-related factors

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Abstract

Background. This study aimed at depicting the course of depression symptoms over the old age, with a special interest in a) uncovering its relationships with sociodemographic and health-related factors; b) analysing its predictive role on healthy-ageing outcomes later in life.

Methods. The sample comprised 8317 older adults (46.02% men) from the English Longitudinal Study of Ageing. Robust structural equation modelling was used to identify symptom trajectories and their relationships with time-varying factors. Trajectory class and covariates were used to predict outcomes (quality of life, satisfaction with life, and daily living functioning) in a 2-year follow-up.

Results. Three trajectory classes (so-called, normative, subclinical, chronic symptom trajectories) were identified for both sexes. Rising hearing difficulties and history of psychiatric problems were consistently associated with the chronic symptom trajectory. Lower education level, history of psychiatric problems, and increasing visual difficulties were connected with the subclinical trajectories. Finally, participants with either a subclinical or a chronic symptom trajectory showed worse outcomes than the remaining participants in the follow-up.

Conclusion: This study highlighted the presence of varying courses of depression symptoms (each showing some distinctive features from other another) over the old age, pointing to some relevant implications for clinical assessment and treatment prescription.

Keywords: Depression; longitudinal trajectories; mixture modelling; healthy ageing; measurement invariance

Introduction

Depression deserves special attention in late life, being one of the most prevalent psychiatric conditions. In the UK, studies have pointed out that almost three in ten people may show clinical levels of depressive symptoms over the old age (Andreas et al., 2017; Braam et al., 2014; Salk et al., 2017). Late-life depression is extensively associated with significant consequences, such as increased mortality, poor daily living functioning and substantial decrease in quality of life (Cuijpers et al., 2013; Damian et al., 2017; Sivertsen et al., 2015). Current models increasingly claim that depression should be tackled at its earliest stages, before full blown symptomatology becomes apparent (Woody & Gibb, 2015). In this sense, studies taking a symptom-level approach have stated the significant impact of clinically subthreshold depression on health-related outcomes over the old age and its individual-specific course (Carriere et al., 2011, 2016; Cuijpers et al., 2013; Salk et al., 2017).

Person-centred methods have highlighted the presence of varying, heterogeneous trajectories of depressive symptoms (Holmes et al., 2017; Hsu, 2012; Kuchibhatla et al., 2012). Recently, a systematic review has provided consistent evidence on depressive symptom trajectories, underlying the overall course, across the lifespan (Musliner et al., 2016). The authors showed that most longitudinal studies identified at least two trajectories of symptoms in the old age: one trajectory comprising most participants (normative trajectory class) and showing low levels of symptomatology; and another trajectory class comprising older adults with rising or persistently high levels of symptoms. However, findings were quite heterogeneous in terms of how many trajectories might exist. A potential explanation of these inconsistencies could be related to divergences either in (see Carriere et al., 2016; Chui et al., 2015; Mirza et al., 2016): assessment protocols (e.g., some studies only approached young-old people), time effect conceptualisation (e.g., symptom trajectories were depicted by assessment wave, but not by age), analytical data approach (i.e., some individual-specific components scarcely approached by several analytical strategies used, such as latent class growth curve or low sample size). Byers et al. (2012) stressed that long-term investigation of depressive symptoms with robust methodology is needed, because most studies so far have been featured by short follow-up periods and overlooking older-old people, subsequently.

Many factors may be involved in how depression symptoms evolve over the old age. The most studied factor is gender. Sex-related differences in depression symptom manifestation and diagnosis rates have been systematically observed, probably because of sexually-mediated biological underpinnings, and socialisation influence (Colman et al., 2007; Salk et al., 2017). In this sense, old women often show higher levels of symptomatology than men, and steeper symptom increases over time (Chui et al., 2015; Hybels et al., 2013; Luppa et al., 2014).

Furthermore, sociodemographic features (i.e., marital status, level of formal education, household income), as well as psychosocial (loneliness, lifestyle behaviour) and health-related factors (history of psychiatric problems, presence of chronic diseases, sensory functioning) may be highly involved in the depiction of the depression symptom course in the late life. For instance, individuals with heightened trajectories of depressive symptoms may show antecedents of psychiatric problems in adulthood, more chronic diseases, basic education and lack of social support (Braam et al., 2014; Carriere et al., 2011; Chui et al., 2015; Hsu, 2012). Unfortunately, most studies have overlooked the time-varying nature of some of these factors over the old age. For instance, it is well known the accumulation of chronic diseases with age and its increasing impact on depression, health-related outcomes and health care service utilisation (Calderon-Larranaga et al., 2018; Olaya et al., 2017; Patten et al., 2018). Also, a rising trajectory of sensory difficulties while becoming older is related to worse functioning and other health-related outcomes over time (Fritze et al., 2016; Lam et al., 2013).

This study aimed to identify heterogeneous longitudinal trajectories of depression symptoms over the old age (65 years and over) in men and women, separately. As highlighted in scientific literature, finding at least two different courses of depressive symptoms for both sexes (i.e., a course featured by low levels of symptoms and another course with rising symptoms over time) would be expected (Musliner et al., 2016). Additionally, it intended to study how some (cross-sectional or time invariant; and time-varying) factors may be related to the identified symptom trajectories. We hypothesised that participants with trajectories with higher levels of symptoms would show psychiatric problems in adulthood and steeper increase in sensory difficulties, as well as multimorbidity and loneliness, than participants comprising other trajectory classes. Finally, we were interested in analysing how trajectory class membership may predict health-related outcomes two years later (quality of life, satisfaction with life and daily living functioning). In this regard, it was expected that participants showing a trajectory of elevated symptoms (even in clinically subthreshold levels) over time would report worse quality of life and satisfaction with life; as well as greater impairment in daily living activities, in comparison to low-symptom trajectories.

Method

Data from the English Longitudinal Study of Ageing (ELSA) were used to satisfy the study aims (NatCen Social Research, 2012; Steptoe et al., 2013). ELSA constitutes an ongoing population-based study comprising surveys every two years (along 14 years so far) since 2002. The target population was people aged 50 or over living in the UK. Refreshment samples were added in waves 3, 4, 6, and 7. By and large, ELSA aims at gathering relevant information on how people age, covering socioeconomic, environmental, and health-related aspects.

Sample

Data from 9483 respondents aged 65-90 years were used. None of them showed a diagnosis of dementia and completed the survey booklets by themselves (see the Supplementary material for further details on sample features). The men's sample comprised 4405 adults (mean age at wave 1 = 73.58, *sd* = 6.42), most of them married at wave 1 (72.65% of respondents), with either no formal qualification (25.39%), or secondary school qualification (25.97%); and mean of household income = £15831.33 a year (*sd* = 13613.45; range = 338654.10). On the other hand, the women's sample was composed of 5078 respondents (mean age at wave 1 = 74.45, *sd* = 6.78), most of them were either married (39.65% of respondents) or widowed (35.85%) at wave 1; with no formal qualification (39.34% of this sample) or secondary school qualification (23.23%); and mean of household income = £12242.69 a year (*sd* = £9370.99; range = 338654.10).

Depression symptoms

Depressive symptomatology was assessed in all waves (Table 1), by means of the Center for Epidemiologic Studies Depression Scale, 8-item version (CES-D 8; Karim et al., 2015; Turvey et al., 1999). This instrument is made up of eight items with a dichotomous (yes/no) scale of response. The CES-D 8 assesses the presence of key symptoms of depression disorders. Although the instrument was not made for depression diagnosis purpose, agreement between the CES-D 8 score and clinical decisions based on standardised psychiatric interviews was well supported in older populations (Karim et al., 2015; Turvey et al., 1999). Thus, a cut-off point for clinical meaningfulness was set at 3 symptoms. Reliability indexes in our sample were appropriate across waves (Kuder-Richardson 20 index between .78 and .81).

Factor profile

Five time-varying factors were studied.

Self-reported health. Respondents graded their overall self-perceived health from 1 (‘excellent’) to 5 (‘poor’) across waves (Table 1).

Multimorbidity. An index consisting of the sum of diagnosed chronic conditions the respondent had was made. Participants reported whether a doctor had ever told them that they have any of these chronic conditions: hypertension, diabetes, cancer, chronic lung disease, arthritis, stroke and heart problems (i.e., angina, myocardial infarction, congestive heart failure, heart murmur, and arrhythmia).

Loneliness. The 3-Item UCLA Loneliness Scale (R-UCLA; Hughes et al., 2004) was used. The scale assesses how often an individual feels a lack of companionship, isolated and left out, by means of three items. Items ought to be responded using a 3-point scale (from ‘hardly ever or never’ to ‘often’). A composite score is obtained from the items. Good reliability indexes were shown for the scale across survey waves (Cronbach’s alpha between .82 and .83).

Hearing and visual function. Participants reported how well they hear (even using a hearing aid), by means of a 5-point scale (from ‘excellent’ to ‘poor’). Also, their impression on their visual functioning (even using visual aids) was reported across waves.

Also, some *time invariant factors* were considered (Table 1): education level, household income, history of psychiatric problems in adulthood (conceptualised as having received mental health treatment for either psychotic symptoms, anxiety, depression or mania) and age of retirement.

Outcomes

Quality of life. The CASP-19 composite score was used to measure quality of life (Hyde et al., 2003). This instrument is made up of 19 items with a 4-point scale of response (from 'often' to 'never'), covering four key domains of quality of life (control, autonomy, pleasure and self-realisation). Reliability index for the CASP-19 was acceptable (Cronbach's α = .89).

Satisfaction with life. The 4-item version of the Satisfaction with Life Scale (SWLS-4; Pavot & Diener, 2008) was used. Each item is responded by means of a 7-point scale of response referring to how much the responder agreed with the item content (from 'strongly disagree' to 'strongly agree'). Reliability index for the SWLS-4 was very good (Cronbach's α = .90).

Activities of daily living. An index accounting for difficulties to perform daily living activities was used (Katz et al., 1963). The index is ranged from 0 (no difficulties) to 6 (difficulties with all six activities). Reliability index for the activities of daily living index (ADL) was acceptable (Kuder-Richardson 20 index = .81).

Instrumental activities of daily living. The Instrumental activities of daily living index (IADL) aims at covering the difficulty a person could show when performing daily living activities necessary for functioning autonomously in community settings (for more details on instrumental activities of daily living, see Lawton, 1971). The index ranges from 0 (no difficulties) to 6 (difficulties with all six activities). The Reliability index for the IADL index was acceptable (Kuder-Richardson 20 index = .83).

Analyses

Latent class mixed modelling (LCMM) was used for trajectory class enumeration (Proust-lima & Jacqmin-Gadda, 2005; Proust-Lima et al., 2017). LCMM allows the study of depression symptom trajectories underlying the overall course (see the Supplementary material). Trajectory class estimation was conducted in the sample of participants who did not show missing data in two consecutive survey waves. Model estimation involves considering the symptom trajectory over time free from the influence of potential covariates that may lead to class overestimation problems (see Diallo, Morin, & Lu, 2016; Vermunt, 2010). Model estimation relied on robust maximum likelihood and full information methods (this enabled the depiction of individual-specific trajectories even when intermittent missing data were present). Criteria to select the model with the optimal class enumeration were: low sample-adjusted Bayesian information criterion (SABIC), mean of posterior probabilities to belong to each class higher than .70; and meaningful proportion of participants within each class (5%).

The sample of participants who responded to at least three out of the four initial waves (from wave 1 to 4) was used to conduct a profile analysis. Multiple imputation methods were used to estimate data when values were missing only in one wave (Brand, 1999). Two methodologies based on measurement invariance (MI) were used for profile analysis (Kievit et al., 2018; Meredith & Teresi, 2006; Widaman et al., 2010): multigroup latent growth curve analysis (MLGC) to study the scores and changes between consecutive waves in factors measured across more than two waves (Table 1); and multigroup change score analysis (MCS) for loneliness. The multigroup factor was the trajectory class membership. Thus, we compared the goodness of fit of structural solutions adding parameter constraints (i.e., in order to make parameter being equal across groups) one at a time (see the Supplementary material for further details).

Model estimation relied on diagonally weighted least squares methods, except for loneliness (i.e., robust maximum likelihood methods). Model fit was studied by the scaled χ^2 statistic, the root mean square error of approximation index of .08 or lower; and comparative fit index (CFI) and Tucker-Lewis index (TLI) higher than .95. Comparisons between the nested MI models were conducted using the incremental CFI (ΔCFI), according to Meade et al. (2008) recommendations. Values of ΔCFI < -.002 would reflect a lack of MI (i.e., trajectory class of symptoms might mediate on levels and/or change across waves).

Multinomial regression was used to study the predictive role of time invariant factors on trajectory class membership. A lower Akaike information criterion (AIC) for the model with profile factors (in comparison to unconstrained models) was expected. *Z*-based Wald tests were used to prove significantly different from zero factor loading. The Cragg and Uhler's R^2 was considered as the effect size estimate.

Finally, generalised linear regression was approached to study outcome prediction (i.e., how trajectory class membership may predict outcomes at wave 6). In this sense, some health-related factors were also included as predictors: latent change scores when a lack of MI was upheld, age at wave 6, history of psychiatric problems and antidepressant prescription at wave 6. Models with covariates were compared to unconstrained models and the related AIC was calculated. *Z*-based Wald tests were also used to prove significance of factor loadings.

All the analyses were conducted using stata (multinomial regression) and R software (R Core Team, 2018) and packages lcmm (trajectory class enumeration), lavaan (measurement invariance analyses) and mice (missing data imputation).

Results

After removing participants with at least two consecutive waves without depression symptom data, sample in analysis comprised 8317 participants (3828 men, with mean initial age = 73.49, *sd* = 6.39; and 4489 women, with mean initial age = 74.26, *sd* = 6.67). Further details and descriptive statistics on relevant factors are included in the Table S1 (see the Supplementary material). Figure 1 displays the flow diagram of sample included in each analysis.

Trajectory class enumeration

The mixture solution comprising three heterogeneous trajectories with linear growth on the fixed and mixture components showed a better fit to data (in comparison to nested models), for both sexes (see the Table S2 in the Supplementary material). Fit indexes were low (SABIC = 36917.51 for men model, SABIC = 50853.62 for women model) and means of posterior probabilities of belonging to each of the three trajectory classes were very good for the men's sample (between .83 to .96) and for the women's sample (between .78 to .91). Thus, most participants comprised the so-called normative trajectory class (77.35% of men and 68.21% of women, respectively), with slight symptom growth over time (time effect with slope, $B = 0.02$, $SE = 0.00$, $p < .05$, for both sexes). Levels of symptoms in participants showing this symptom trajectory remained low over time (never approaching the level of clinical meaningfulness). Also, a trajectory class (the so-called subclinical trajectory class) comprising individuals with increasing levels of symptoms was found (16.64% of men and 21.25% of women, respectively). Symptoms surpassed the cut-off point of clinical meaningfulness over time in this class (time effect with slope, $B = 0.04$, $SE = 0.00$, $p < .05$, for men; and $B = 0.03$, $SE = 0.00$, $p < .05$, for women). Finally, it identified a class (the so-called chronic symptom trajectory class) of participants (6.01% of men and 10.54% of women) who showed heightened levels of symptoms over time (see Table S3 for factor loadings within each class). Symptom level remained clinical and stable over time (as no time effect was found, with $p > .05$, for both sexes) in this class. Sex-specific trajectories by class are displayed in the Figure 2.

Factor profile

In order to check the absence of overlap between morbidity and sensory function and depression symptoms in old age, correlation analyses were conducted. As a result, weak correlations were observed across waves: Pearson's *r* from .16 at wave 3 and .22 at wave 1, regarding the multimorbidity index and CES-D 8; Spearman's ρ between .15 (CES-D 8 at wave 1 and visual function at wave 4) to .23 (CES-D 8 at wave 5 and visual function at wave 4), for the relationship between depression symptoms and vision; and Spearman's ρ between .06 (CES-D 8 at wave 1 and hearing function at wave 4) to .14 (CES-D 8 at wave 5 and hearing function at wave 4), for the relationship between depression symptoms and hearing.

MI models revealed significantly different growth slopes across trajectory classes in both sexes, as proven by the lack of MI observed only when the latent variable slope (related to changes between consecutive waves) was constrained (see Table S4). Regarding the men's sample, participants comprising the chronic symptom trajectory class showed steeper growth in multimorbidity ($B = 0.27$, $SE = 0.05$; $z = 5.75$, $p < .01$) and hearing difficulties ($B = 0.12$, $SE = 0.05$; $z = 2.23$, $p < .03$); as well as higher decrease in loneliness ($B = -0.50$, $SE = 0.17$; $z = -2.97$, $p < .01$). Men from the subclinical trajectory class exhibited a stronger growth of visual difficulties ($B = 0.10$, $SE = 0.02$; $z = 4.19$, $p < .01$) than those from the other classes (see Figure 3).

On the other hand, women from the chronic symptom trajectory class showed a steeper rising of hearing difficulties ($B = 0.10$, $SE = 0.03$; $z = 3.17$, $p < .01$) than those from the other classes; subclinical trajectory class women displayed a higher increase of multimorbidity ($B = 0.21$, $SE = 0.01$; $z = 17.38$, $p < .01$) and visual difficulties ($B = 0.10$, $SE = 0.02$; $z = 4.90$, $p < .01$). Finally, normative class participants showed a higher growth rate in self-reported health ($B = 0.12$, $SE = 0.01$; $z = 11.21$, $p < .01$).

Multinomial regression revealed that the predictive role of cross-sectional profile factors on class membership for both sexes (model for men, with AIC = 508.71 and $R^2 = 0.11$; and for women, AIC = 766.97 and $R^2 = 0.06$) than the unconstrained models (AIC

= 1541.64 and R^2 = 0.00, for men; AIC = 2925.80 and R^2 = 0.00, for women). The subclinical class membership was explained by the history of psychiatric problems (relative risk ratio = 9.82, *CI95* = 3.27, 29.47; z = 4.07, p < .01) in men. On the other hand, the subclinical class membership in the female sample was explained by the household income (relative risk ratio = 0.99, *CI95* = .99, 1.00; z = -2.19, p < .03). No significant cross-sectional predictors were related with the clinical trajectory class membership for both sexes.

Outcome prediction

Generalised linear regressions revealed that quality of life at wave 6 was significantly explained by an intercept, the class membership and age at wave 6 in both sexes (see Table 2). The antidepressant prescription also showed a significant explanatory role on this outcome for women. Satisfaction with life was explained in male participants by the intercept, trajectory class membership and age at wave 6. Conversely, this outcome was only explained by the intercept and class membership.

Regarding functioning outcomes, ADL in male sample was explained by the intercept and changes in loneliness across waves; and IADL by trajectory class membership and age at wave 6. On the other hand, ADL and IADL was explained by class membership, age and antidepressant prescription in the sample of female respondents (Table 2). It is worth mentioning that antidepressant prescription was significantly different across trajectory classes only in the sample of female older people, χ^2 (2) = 15.48, p < .01 (24.61% of women from the chronic symptom trajectory class had antidepressant prescription, in comparison with 13% and 9% of those from the subclinical and normative classes, respectively). Figure 4 displays how outcomes were distributed across trajectory class membership.

Discussion

This study aimed to provide some evidence on how depression symptoms evolve in old age. Relying on longitudinal person-centred methods, it intended to identify heterogeneous trajectories for both sexes. Moreover, we were interested in studying the relationship between some sociodemographic and health-related factors (factor profile), highly connected with depression disorders, and sex-specific trajectories. Finally, it aimed to study how the varying longitudinal courses of symptoms might explain healthy-ageing outcomes (quality of life, satisfaction with life, ADL and IADL), later in life.

Findings derived from this study highlighted that since depression symptoms were increasingly higher over time, heterogeneous trajectories should be considered. Concretely, we identified three different trajectories of symptoms for both men and women (i.e., the so-called normative, subclinical symptom and chronic symptom trajectories). Our results go in line with some assumptions already well-supported in scientific literature (Carriere et al., 2016; Kaup et al., 2016; Luppa et al., 2014; Montagnier et al., 2014; Musliner et al., 2016): 1) sex-specific differences in trajectory membership (i.e., more proportion of women showing subclinical and chronic symptom trajectories in comparison to men); 2) most of the participants showed low levels of symptoms (more than 65% in our samples); 3) chronic symptomatology was quite infrequent among old people (6.01% of men and 10.54% of women). Interestingly, participants depicting a chronic symptom trajectory showed heightened levels of symptoms over the old age (and probably in earlier periods of life). The other trajectory classes showed increasing levels of symptoms over time.

Regarding the factor profile, the history of psychiatric problems was proved to be consistently associated with rising symptom trajectories, in line with other studies (Carriere et al., 2016; Hsu, 2012; Montagnier et al., 2014; Musliner et al., 2016).

Moreover, we found that chronic symptom trajectory class membership was associated with a higher increase in hearing difficulties and multimorbidity, probably because of reward loss on a daily basis (e.g., difficulty in holding conversations), regardless of sex (Brewster et al., 2018; Rote et al., 2015). On the other hand, subclinical trajectory class membership was distinguished by a higher increase in visual difficulties over time probably due to a moderate loss of reward (i.e., visual impairment limits independence) and sensory disability (Freeman et al., 2016; Tolman et al., 2005).

Interestingly, sex-specific relationships with some factors and symptom trajectories were found. In women, a higher amount of multimorbid conditions over time was linked with showing a rising symptom trajectory. Robust studies have shown a strong relationship between the onset of depression syndromes and multimorbidity, especially related to disease management and functional and social role losses (Carayanni et al., 2012; Chui et al., 2015; Marengoni et al., 2011).

Regarding men, a higher number of multimorbid conditions over time was related to chronic symptom trajectory class membership. Feelings of being less useful on a community and family (i.e., difficulty in multimorbidity management) bases seem to have a crucial role on maintaining heightened depression symptomatology in men. Additionally, old men may show many difficulties to adjust themselves to live alone due to widowhood and feelings of loneliness may emerge. For that reason, they tended to look for a new partner more frequently than women (see Girgus et al., 2017). Our results in loneliness changes across waves may go in this line: the proportion of men who were widowed in wave 3 (3.95%) was slightly higher in comparison to wave 4 (3.64%); conversely, the proportion of men with a civil partner rose from wave 3 (0.82%) to wave 4 (1.29%).

Finally, this study provided some valuable evidence on how depression symptom trajectory would have an impact on some healthy-ageing outcomes later in life, even after controlling for profile factors and age. We found that participants, regardless of sex, with either a chronic symptom or subclinical trajectory manifested lower quality of life and satisfaction with life than normative-trajectory participants; they also manifested higher ADL (only women) and IADL difficulties. This goes in line with the idea of overcoming traditional diagnosis-based approaches and addressing psychiatric conditions from earlier stages (Woody & Gibb, 2015; Schoevers et al., 2006). Subthreshold depression is responsible for changes in brain structures involved in emotion and cognition, and may be a risk factor for severe diseases and increased mortality (Chang et al., 2017; Cuijpers et al., 2013; Zhou et al., 2016).

To summarise, this study aimed at uncovering the heterogeneous, person-specific nature of depression symptom course throughout the late life period. Our results relied on a robust, longitudinally-based methodology (i.e., trajectories modelled by means of age and time-varying profile factors were addressed), with a large sample of a nationally representative cohort of older adults. Furthermore, trajectories were modelled by sex. Finally, trajectory class enumeration was based on latent constructs and not on pre-established, arbitrary conceptualisations.

On the other hand, this study had some shortcomings worth mentioning. Firstly, study variables were taken from self-reported items. Self-reported symptoms and health conditions have been shown as reliable proxies of actual states and diagnoses, but some considerations should be taken to ensure their accuracy (see Pettersson et al., 2015; Stockings et al., 2015; Stone et al., 2000). In this sense, we reported psychometric properties of the self-reports used in this study, stating adequate levels of validity and reliability. However, further research should be done with objective tests in order to complement findings from this study. Furthermore, cognitive decline was not assessed in our sample. This may be associated with depression symptoms. In this sense, we came from a free-dementia sample, discarding the effect of severe cognitive decline on our data. However, stronger controls on cognitive decline should be taken in further research. Also, factor profile and prediction outcome analyses comprised lower sample size in comparison to class enumeration ones. In this regard, no missing data is permitted across waves when modelling MI solutions and generalised regression. However, attrition analyses showed no significant differences between respondent and non-respondent participants in terms of sociodemographic and health-related factors. On the other hand, the use of aids (e.g., hearing aids, glasses) was not recorded in this study. Even though, we were interested in studying the impact of sensory disability on a daily basis (for that reason, assessing individual's impression on sensory functioning even using aids). The use of aids is common in western countries and almost available to everyone. Therefore, aids enable functional independence being recovered (or at least, partially) and sensory function improved.

Depression is a global health priority. This study constitutes an attempt to raise awareness of personalised medicine and its potential. For that reason, very useful implications in terms of clinical assessment and treatment prescription may be derived. Firstly, a mention on tailored protocols is mandatory. We identified different symptom trajectories and related profile factors. Clinicians and researchers should consider person-specific and longitudinal issues to make decisions on diagnosis and clinical profiles more accurate. In this regard, a patient showing depression symptoms due to, for instance, the death of a relative and low level of community participation may present a very characteristic profile in comparison to a person exhibiting depression symptoms chronically. Therefore, therapeutic choice should be guided by patient profile. Moreover, therapeutic options addressing modifiable health-related factors (e.g., sensory aids or behavioural interventions promoting healthy lifestyles) may hinder the escalation of depression symptoms across the old age. Secondly, prevention (e.g., initiatives aimed at raising the awareness of the importance of healthy eating and adequate exercise in the middle age) should be a lifelong imperative to prevent the burden of depression in the old age and its related impact. Finally, clinicians and health and social policy makers should make higher efforts to deal with late-life depression from earlier syndromic states due to its prevalence (almost 25% of older adults reached clinically meaningful symptoms over the course of their lifetime) and impact on quality of life and daily functioning.

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Conflict of interests: none.

Availability of data and materials

Data are available on ELSA webpage (http://elsa-project.ac.uk). Details on complementary analyses and results are available upon corresponding author request.

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***Table 1.* Timetable of the ELSA study across survey waves.**

	Wave 1 (2002/03)	Wave 2 (2004/05)	Wave 3 (2006/07)	Wave 4 (2008/09)	Wave 5 (2010/11)	Wave 6 (2012/13)
Depression symptoms*	X	X	X	X	X	
Profile factors						
Self-reported health	X	X		X		
Multimorbidity	X	X	X	X		
Loneliness**			X	X		
Hearing function	X	X	X	X		
Visual function	X	X	X	X		
Education level•	X					
Household income	X					
History of psychiatric problems	X					
Age of retirement					X	
Outcomes						
Quality of life†						X
Satisfaction with life‡						X
ADL						X
IADL						X

Note. * Measured by the Center for Epidemiologic Studies Depression Scale, 8-item version (CES-D 8); ** Measured by the 3-Item UCLA Loneliness Scale (R-UCLA).

• Categories considered: no qualification mentioned; up to secondary school; secondary school graduate; some college education; college graduate or above.

† Assessed by the CASP-19 questionnaire; ‡ Assessed by the 4-item version of the Satisfaction with Life Scale (SWLS-4).

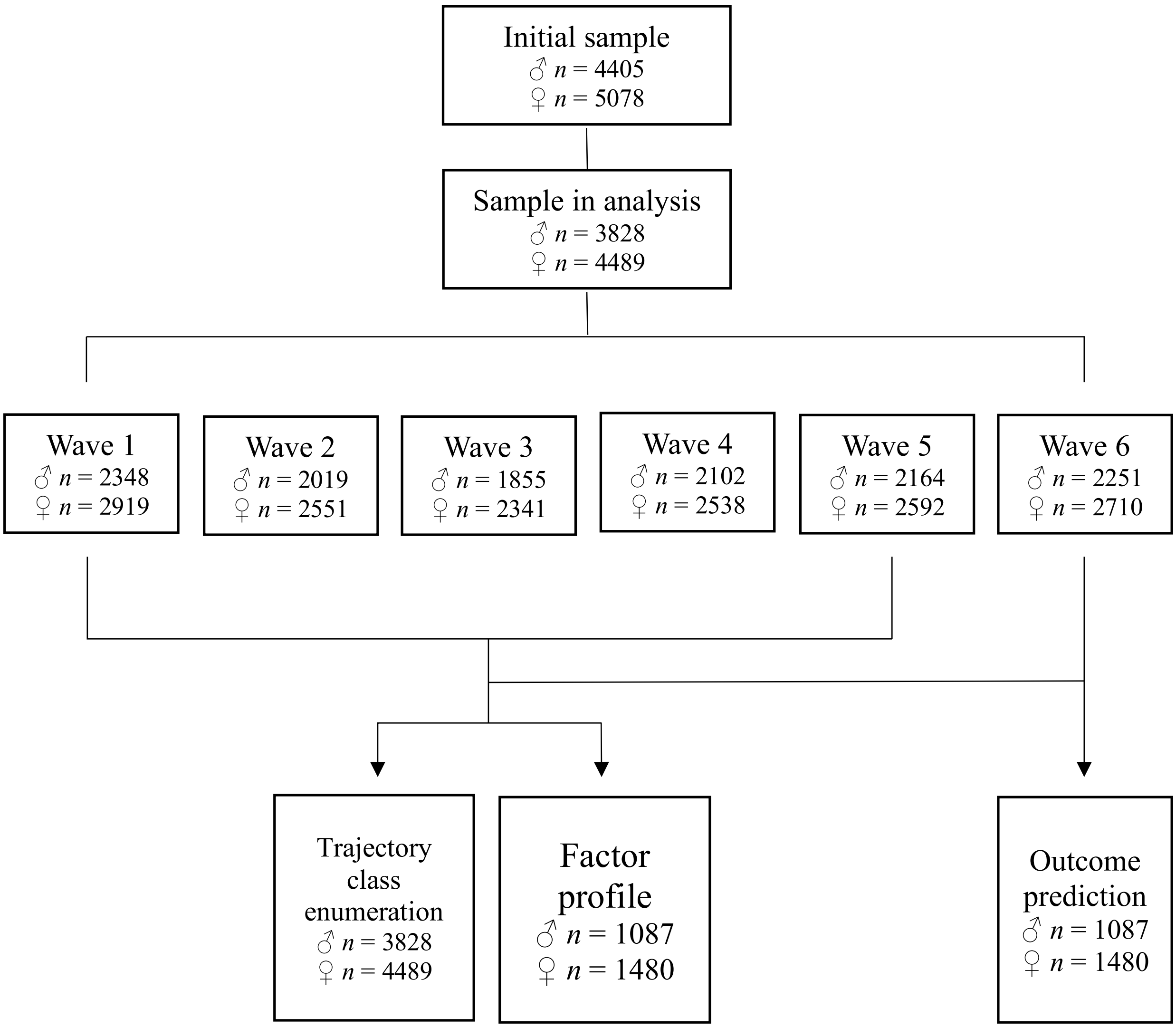
ADL = Activities of daily living; IADL = Instrumental activities of daily living.

***Table 2.* Outcome prediction (at wave 6) according to sex.**

Predictor	Men				Women			
	Quality of life	Satisfaction with life	ADL	IADL	Quality of life	Satisfaction with life	ADL	IADL
(Intercept)	72.76 (11.12)***	52.12 (8.32)***	-2.63 (0.70)***	-1.15 (0.71)	61.46 (7.67)***	30.31 (5.79)***	-0.71 (0.56)	-1.97 (0.52)***
Trajectory class membership								
Linear effect	-5.06 (1.21)***	-4.33 (0.98)***	0.12 (0.09)	0.12 (0.09)	-4.29 (0.71)**	-2.91 (0.55)**	0.20 (0.05)***	0.23 (0.05)***
Quadratic effect	5.16 (4.41)	0.83 (3.35)	-0.18 (0.33)	-0.89 (0.09)**	8.03 (1.44)**	5.18 (1.01)	-0.34 (0.09)***	-0.28 (0.08)**
Age at wave 6	-0.48 (0.13)***	-0.36 (0.10)***	0.04 (0.01)***	0.02 (0.01)*	-0.32 (0.09)***	-0.09 (0.01)	0.02 (0.01)*	0.03 (0.01)***
Antidepressant prescription	-0.52 (2.13)	1.02 (1.66)	-0.02 (0.16)	0.23 (0.16)	-3.28 (1.57)*	-1.17 (1.12)	0.30 (0.10)**	0.25 (0.09)**
Household income†					-0.01 (0.01)	-0.00 (0.01)	-0.00 (0.01)	-0.00 (0.01)
Psychiatric history†	3.60 (3.24)	4.23 (2.47)	-0.09 (0.24)	-0.14 (0.24)				
Loneliness change†‡	0.54 (0.75)	0.05 (0.60)	-0.15 (0.05)**	0.04 (0.05)				
Hearing difficulty change‡	3.81 (7.88)	2.31 (5.98)	0.19 (0.53)	0.49 (0.54)	-6.66 (4.09)	0.19 (3.11)	0.04 (0.30)	0.06 (0.28)
Visual difficulty change‡	-5.13 (7.72)	1.58 (5.85)	0.40 (0.53)	0.93 (0.54)	-0.36 (2.96)	-1.50 (2.23)	0.10 (0.22)	0.20 (0.20)
Multimorbidity change‡	0.86 (2.33)	0.02 (1.76)	0.01 (0.16)	-0.16 (0.16)	-2.31 (1.55)	-0.41 (1.17)	-0.05 (0.11)	-0.01 (0.10)

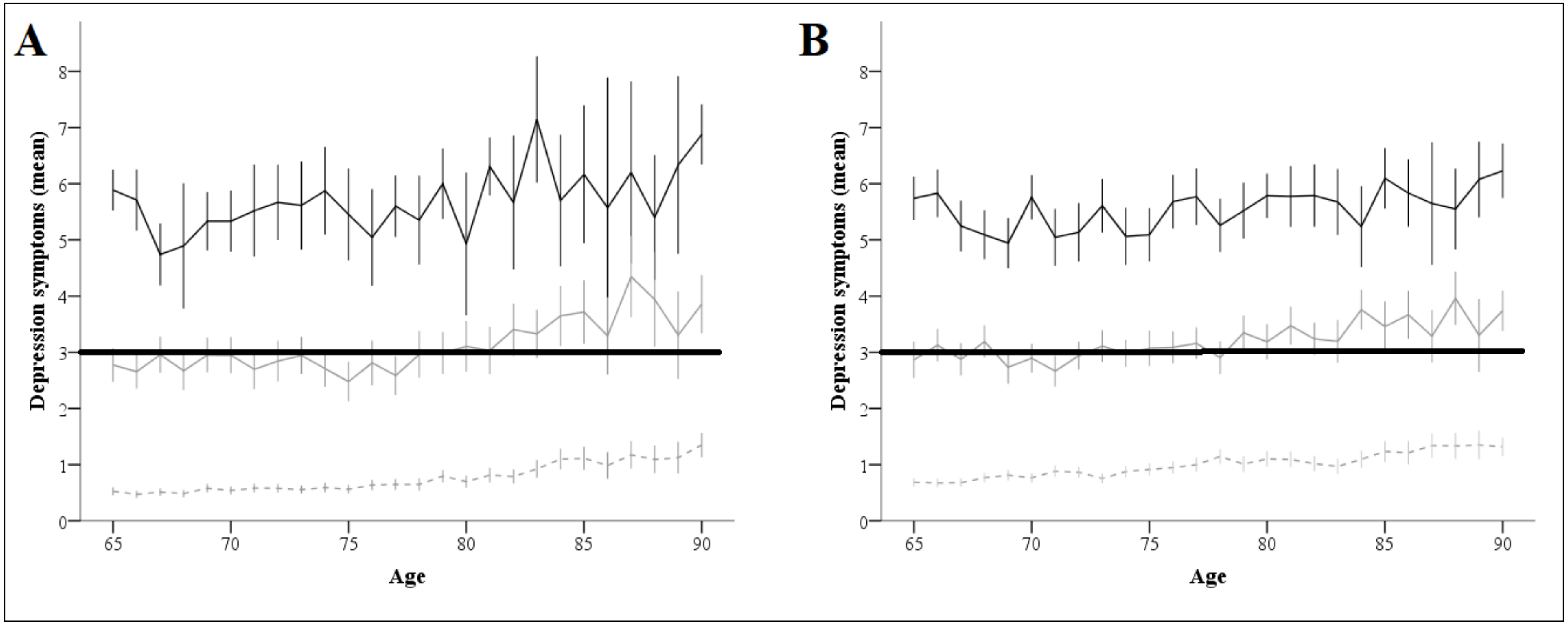
Note. Factor loading and standard error (between brackets) are displayed by outcome.
Quality of life was assessed by the CASP-19 questionnaire. Satisfaction with life was assessed by the 4-item version of the Satisfaction with Life Scale (SWLS-4). ADL = Activities of daily living. IADL = Instrumental activities of daily living.
† Factors that showed sex-specific different scores across depression trajectory classes
‡ Latent scores of change across waves (taken from the measurement invariance models).
* $p < .05$; ** $p < .01$; *** $p < .001$.

***Figure 1.* Flow diagram of sample included in analyses.**



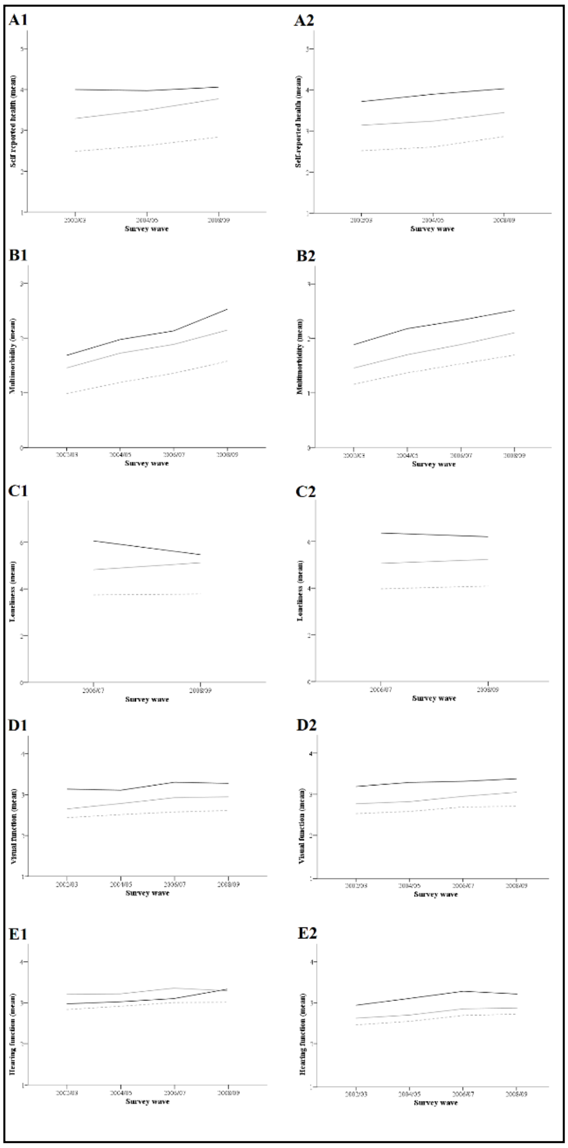
Note. ♂ = sample of men. ♀ = sample of women.

Figure 2. **Class-specific trajectories of depression symptoms by sex.**



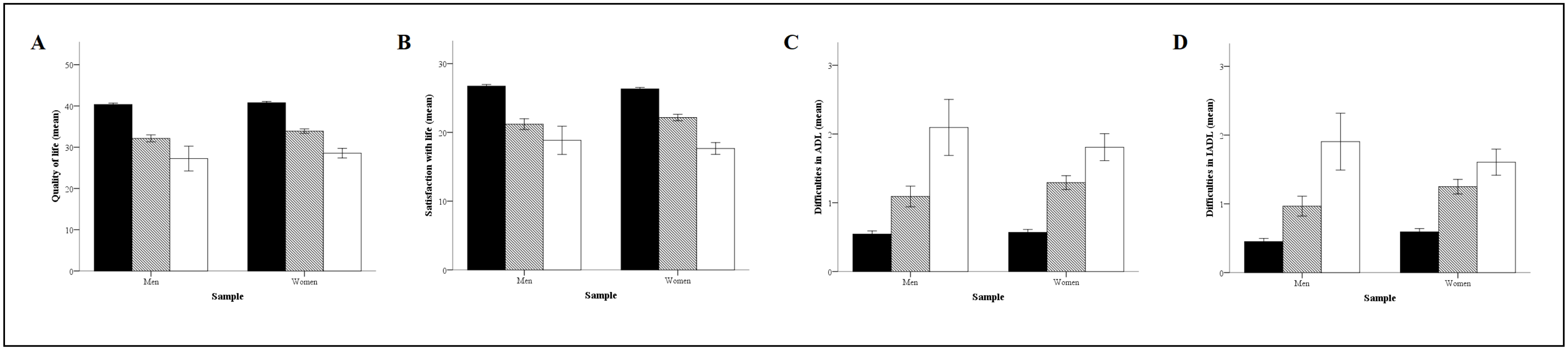
Note. The A box displays the class-specific trajectories for male participants. The B box displays the class-specific trajectories for female participants.
Thick dark line depicts the cut-off point for clinical meaningful level of symptoms (CES-D 8 ≥ 3 involves clinical levels of symptomatology according to Turvey et al., 1999).
Error bars depict the 95% confidence interval of the mean.
Dashed grey line = normative trajectory class. Solid grey line = subclinical trajectory class. Solid dark line = chronic symptom trajectory class.

Figure 3. **Class-specific trajectories of time-varying risk factors by sex.**



Note. Boxes A = class-specific trajectories of self-reported health (from 1, ‘excellent’, to 5 ‘poor’). Boxes B = trajectories of multimorbidity across survey waves. Boxes C = trajectories of loneliness across waves. Boxes D = class-specific trajectories of self-reported visual function (from 1, ‘excellent’, to 4 ‘poor’). Boxes E = trajectories of self-reported hearing function (from 1, ‘excellent’, to 4 ‘poor’).
Boxes 1 = trajectories for male participants. Boxes 2 = trajectories for female participants. Dashed grey line = normative trajectory class (*n* = 1021, for the male sample; *n* = 1149, for the female sample). Solid grey line = subclinical trajectory class (*n* = 216, for the male sample; *n* = 436, for the female sample). Solid dark line = chronic symptom trajectory class (*n* = 45, for the male sample; *n* = 157, for the female sample).
Error bars are not provided due to overlapping between scores across classes.

Figure 4. **Class-specific scores of outcomes measured at wave 6 by sex.**



Note. Box A = class-specific scores in quality of life. Box B = class-specific scores in satisfaction with life. Box C = class-specific scores in difficulties in activities of daily living (ADL). Box D = class-specific scores in difficulties in instrumental activities of daily living (IADL).
Error bars depict the standard error of the mean.
Dark bar = normative trajectory class participants (n = 719, for the male sample; n = 817, for the female sample). Grey bar = subclinical trajectory class participants (n = 120, for the male sample; n = 300, for the female sample). White bar = chronic symptom trajectory class participants (n = 21, for the male sample; n = 99, for the female sample).
Significant differences were found in all the outcomes between the participants from the clinical classes and those from the normative classes ($p < .01$); and between the participants from the clinical classes and those from the normative classes (p <